Mild Synthesis of β-Amino-α,α-difluoro Ketones from Acylsilanes and Trifluoromethyltrimethylsilane in a One-Pot Imino Aldol Reaction[‡]

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β-Amino-α,α-difluoro ketones have been very conveniently prepared in a one-pot procedure from acylsilanes, trifluoromethyltrimethylsilane and imines. The key intermediate in this reaction is a difluoroenoxysilane. The Lewis acid promoted imino aldol reaction was performed with $BF_3{\cdot}OEt_2$ or under very mild conditions using a catalytic amount of $Yb(OTf)_3$. The reaction with chiral benzylimines occurred in good yield with 52–78% *de*. Palladium-catalyzed hydrogenolysis furnished an unprotected β-amino-α,α-difluoro ketone or a β-amino-α,α-difluoro alcohol.

Introduction

The introduction of fluorine atoms into a molecule often produces significant changes in its physical, chemical and biological properties.[1] For example, the insertion of the β-amino-α,α-difluoro ketone unit into a peptide proved to be successful in the design of enzyme inhibitors such as protease inhibitors. The mechanism postulated for their biological activity involves the hydration of or hemiketal formation from the carbonyl group to provide a stable tetrahedral analogue of the transition state formed in peptide-bond cleavage reactions.[2] In spite of the interest in β-aminodifluoro ketones, only a few methods have been reported for their synthesis. They have been prepared by Reformatsky addition[3] or reductive coupling reactions[4] of α-halodifluoro ketones to imines, by intramolecular [3,3] rearrangement of difluoroallylic alcohols[5] and by the reaction of difluoroenol methyl ethers[6] or difluoroenol silyl ethers[7,8] with *N*-acyliminiums or imines under Lewis acid activation. However, in the latter method, difluoroenol silyl ethers have to be isolated, but these compounds are not easily prepared from aliphatic compounds.

In recent years we have demonstrated the utility of a three-component system involving an acylsilane, trifluoromethyltrimethylsilane (TFMTMS) and an electrophile in the synthesis of various α,α-difluorocarbonyl compounds.[9] The major advantage of this one-pot method is that the intermediate difluoroenol silyl ether does not need to be isolated and the α,α-difluorocarbonyl compounds are obtained in high yield from a wide variety of acylsilanes. We report herein a new application of this strategy to the one-pot synthesis of β-amino-α,α-difluoro ketones.

Results and Discussion

According to our procedure, the difluoroenoxysilanes were generated in situ from acylsilanes **1** and **2** and trifluoromethyltrimethylsilane (TFMTMS) in dichloromethane by fluoride initiation (Table 1). Various substituted aldimines **3** were then added to the solution and, under Lewis acid activation the corresponding β-amino-α,α-difluoro ketones **4** and **5** were produced. Unlike non-fluorinated enoxysilanes,[10] difluoroenoxysilanes proved to be unreactive with *N*-arylbenzaldimine **3a** in the presence of a catalytic amount of $Yb(OTf)_3$ or TMSOTf or with a stoichiometric amount of triflic acid (Table 1, entries 1–3). Only trace amounts of β-amino ketone **4b** were obtained from the *N*-benzylbenzaldimine **3b** under catalytic $Yb(OTf)_3$ or TMSOTf activation demonstrating the poor regeneration of the catalytic activating species (Table 1, entry 4). The β-amino ketone **4b** was obtained in a better yield by using 2 equiv. of $BF_3{\cdot}OEt_2$ as the Lewis acid (Table 1, entry 5). In a similar manner, the aliphatic imine **3c** afforded the corresponding β-amino ketone **4c** in 46% yield. The *N*-ethoxycarbonylimine **3d** proved to be much more reactive, giving the β-amino ketones **4d** and **5d** in 82 and 70% yields, respectively, from reactions with the aromatic acylsilane **1**

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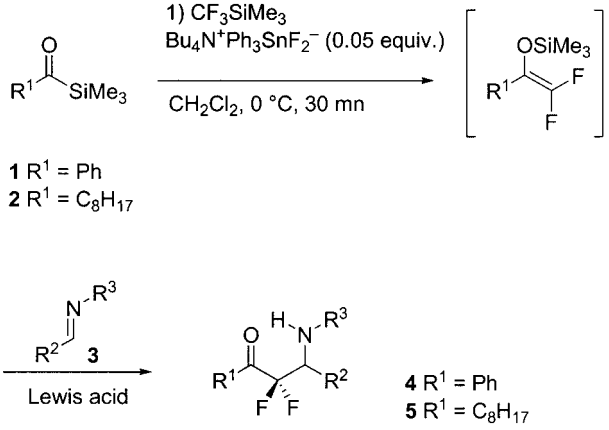
Table 1. One-pot imino aldol reaction of acylsilanes **1** and **2**, trifluoromethyltrimethylsilane and imine **3**.



Entry	Acylsilane	Imine[a]	R^2	R^3	Lewis acid (equiv.)	Product	Yield [%][b]
1	**1**	**3a**	*p*MeOPh	*p*MeOPh	$Yb(OTf)_3$ (0.2)		no reaction
2	**1**	**3a**	*p*MeOPh	*p*MeOPh	TMSOTf (0.15)		no reaction
3	**1**	**3a**	*p*MeOPh	*p*MeOPh	CF_3SO_3H (1.1)[c]		no reaction
4	**1**	**3b**	Ph	Bn	$Yb(OTf)_3$ (0.2)	**4b**	traces[d]
5	**1**	**3b**	Ph	Bn	$BF_3{\cdot}OEt_2$ (2)	**4b**	36
6	**1**	**3c**	Et	Bn	$BF_3{\cdot}OEt_2$ (2)	**4c**	46
7	**1**	**3d**	Ph	CO_2Et	CF_3SO_3H (1.1)[c]	**4d**	82
8	**2**	**3d**	Ph	CO_2Et	CF_3SO_3H (1.1)[c]	**5d**	70
9	**1**	**3d**	Ph	CO_2Et	$Yb(OTf)_3$ (0.2)	**4d**	58
10	**1**	**3d**	Ph	CO_2Et	TMSOTf (0.1)	**4d**	72
11	**1**	**3e**	Ph	*t*-Boc	$Yb(OTf)_3$ (0.2)	**4e**	44
12	**2**	**3e**	Ph	*t*-Boc	$Yb(OTf)_3$ (0.2)	**5e**	70

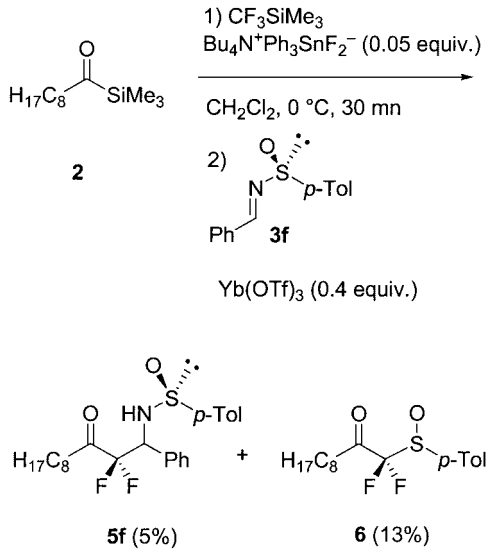
[a] 1.2 equiv. [b] Isolated yields of pure compound based on **1** or **2**. [c] Triflic acid was added to the imine in order to form the iminium salt before addition of the difluoroenoxysilane. [d] Trace amounts of **4b** were also obtained with TMSOTf (0.2 equiv.) as the Lewis acid.

and the aliphatic acylsilane **2** in the presence of a stoichiometric amount of triflic acid (Table 1, entries 7 and 8). The one-pot imino aldol reaction of this activated imine **3d** was also efficiently performed under very mild conditions by using a catalytic amount of $Yb(OTf)_3$ or TMSOTf as the Lewis acid at room temperature (Table 1, entries 9 and 10). In order to anticipate a convenient removal of the imine activating group, the reactivity of the *N*-Boc-benzaldimine **3e** was studied. The one-pot imino aldol reactions of the difluoroenoxysilanes prepared from the acylsilanes **1** and **2** with the imine **3e** also occurred in very mild conditions at room temperature with $Yb(OTf)_3$ as the catalyst to give the corresponding *N*-Boc-amino ketones **4e** and **5e**.

The diastereoselective addition of nucleophiles to imines derived from aldehydes and chiral amines is a useful method for the preparation of optically active secondary amines. In order to study the stereoselectivity of the reaction of difluoroenoxysilanes with chiral imines, we first examined the reaction of the aliphatic difluoroenoxysilane prepared from **2** with the chiral sulfinylimine **3f**[11] (Scheme 1). No reaction occurred without activation by a Lewis acid. Unfortunately, the $Yb(OTf)_3$-mediated reaction furnished the expected β-amino ketone **5f** in a very low yield (5%). The major product of the reaction was the difluoromethyl ketone resulting from the hydrolysis of the difluoroenoxysilane. Furthermore, the formation of the fluorinated sulfoxide **6** (13%) suggests that attack at the sulfur atom occurs as a side-reaction. Note that these fluorinated β-ketosulfoxides are rarely reported in the literature.[12] The reaction promoted by $BF_3{\cdot}OEt_2$ did not produce better results; the sulfoxide **6** was isolated in a low yield (14%) and the expected β-amino ketone was not formed.

Chiral aldimines prepared from (*R*)- or (*S*)-α-methylbenzylamine and aldehydes are frequently used as precursors in the stereoselective synthesis of chiral amino compounds. Some examples of the reactions of these imines with silyl ketene acetals to give β-amino esters have been reported in the literature.[13] Nevertheless, to the best of our knowledge, their imino aldol reactions with a silyl enol ether, resulting in the corresponding β-amino ketones, have not been described. In the fluorinated series, the reaction of the difluoroenoxysilane derived from the aromatic acylsilane **1** with the (*R*)-benzaldimine **3g** in the presence of $BF_3{\cdot}OEt_2$ gave the corresponding β-amino ketone **4g** in 53% yield and with a 76:24 diastereomeric ratio (Table 2). Under the same conditions, the reaction of the aliphatic acylsilane **2** furnished the β-amino ketone **5g** in 83% yield and with a higher stereoselectivity (89:11 diastereomeric ratio). The one-pot imino aldol reaction of **2** with the (*R*)-isopropylimine **3h** gave **5h** in 55% yield as a 87:13 mixture of diastereomers.

The absolute configuration of the major diastereomers of **4g** and **5g** is anticipated to be (*R*,*S*) on the basis of the ^1H NMR chemical-shift measurements. Yamamoto and co-



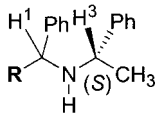
Scheme 1. One-pot imino aldol reaction using the enantiopure sulfinylimine **3f**.

workers reported detailed ^{1}H NMR spectroscopic data for the (*R*,*S*) and (*S*,*S*) β-amino *tert*-butyl esters derived from (*S*)-benzaldimine.[13d] In the fluorinated series Pirkle et al.[14] and Uno et al.[15] gave similar data for the perfluoalkylated analogues. As already mentioned by Uno et al., for all these compounds, the *anti* relative configuration of the H^1 and H^3 atoms was accompanied by a shielding of the H^1 atom due to the phenyl group of the phenethyl moiety (Table 3).

As we started with the (*R*)-benzaldimine **3g** and as we observed a 0.5 ppm upfield shift of the H^1 proton in the minor diastereomers of **4g** and **5g**, we assign the (*S*,*R*) configuration to these minor diastereomers (Figure 1). The configurations of the **5h** diastereomers could not be assigned by using the same NMR argument. The major diastereomers of **5g** and **5h** were isolated in a pure form after column chromatography.

The one-pot imino aldol reaction was then extended to the (*R*)-phenylglycinol-derived oxazolidine **3i** and the silylated imine **3j** in order to evaluate the effect of an heteroatom in the chiral side-chain on the stereoselectivity of the reaction (Scheme 2). Under the standard conditions, the reactions of the difluoroenoxysilanes derived from the acylsilanes **1** and **2** with **3i** gave the β-amino ketones **4i** (63% yield, 79:21 diastereomeric ratio) and **5i** (73% yield, 65:35 diastereomeric ratio), respectively. The diastereoselectivity of these reactions was not improved by generating an intermediate chiral iminium ion. However the stereoselectivity of the reaction of the aromatic difluoroenoxysilane was increased by using the silylated imine **3j** which gave the amino

Table 3. Literature NMR spectroscopic data for (*S*)-1-phenylethylamine-based benzaldimine addition products.



R	(H^1,H^3) relative configuration	δ(H^1) [ppm]	Ref.
*t*BuOCOCH$_2$	*syn*	4.14	[13d]
	anti	3.73	
C_3F_7	*syn*	4.35	[14]
C_6F_{13}	*syn*	4.37	[15]
	anti	4.00	

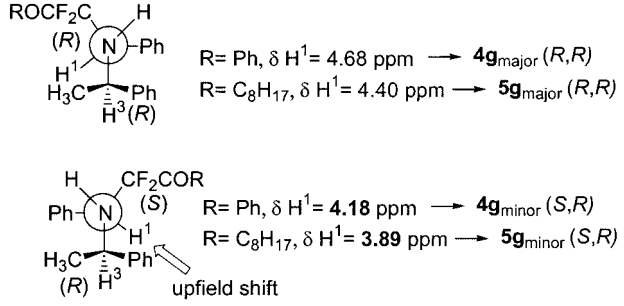
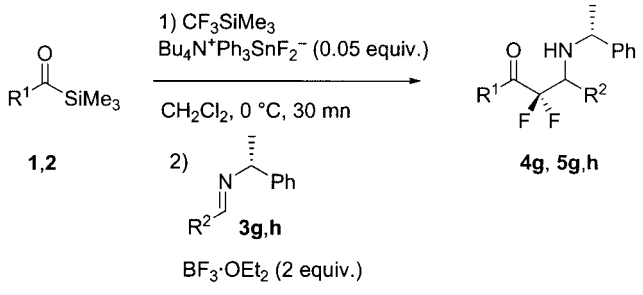


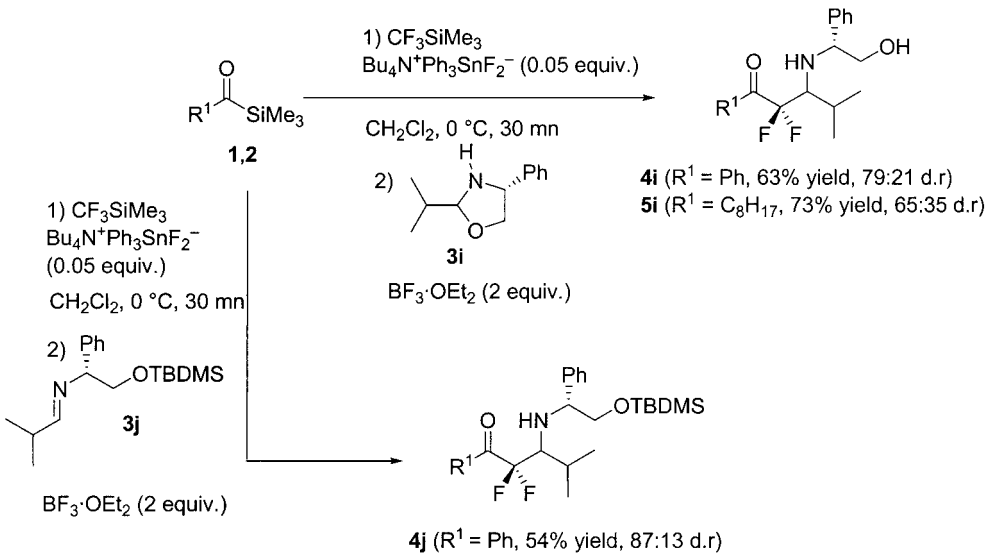
Figure 1. ^{1}H NMR chemical shift measurements of H^1 in **4g** and **5g**.

Table 2. One-pot imino aldol reactions using chiral aldimines **3g**,**h**.



Entry	Acylsilane	R^1	Aldimine[a]	R^2	Product	Yield [%][b]	*dr*[c]
1	**1**	Ph	**3g**	Ph	**4g**	53	76:24
2	**2**	C_8H_{17}	**3g**	Ph	**5g**	83	89:11
3	**2**	C_8H_{17}	**3h**	*i*Pr	**5h**	55	87:13

[a] 1.2 equiv. [b] Isolated yields of pure compound based on **1** or **2**. [c] Determined from the ^{19}F NMR spectrum of the crude mixture.



Scheme 2. One-pot imino aldol reactions with the (*R*)-phenylglycinol-derived oxazolidine **3i** and imine **3j**.

ketone **4j** in 54% yield and with a 87:13 diastereomeric ratio.

We then investigated the removal of the chiral auxiliary from the amine by palladium-catalyzed hydrogenolysis.[16–18]

The hydrogenolysis of the β-amino ketone **5h** was carried out at room temperature under an atmospheric hydrogen pressure in the presence of Pd/C in methanol or ethyl acetate (Table 4, entries 1 and 2). Under these conditions, both debenzylation and reduction of the carbonyl group occurred to give the β-amino alcohol **7** in high yield. The relative configurations of the two diastereomers of **7** could not be assigned. A similar total reduction of **5h** occurred in methanol even in the presence of $Pd(OH)_2$ which is known to favour benzylic hydrogenolysis (Table 4, entry 3). The high efficiency of the reduction of the α-difluorocarbonyl group in very mild conditions should be underlined. Usually, this reaction requires the use of a ruthenium,[19] rhodium[20] or platinum[21] catalyst under hydrogen pressure. The reduction of the carbonyl group could be avoided by using $Pd(OH)_2$ in a non-protic solvent such as ethyl acetate. Under these conditions, the expected unprotected β-amino-α,α-difluoro ketone **8** was obtained in a high yield (Table 4, entry 4). This amino ketone proved to be unstable to silica gel chromatography giving the imine **9** in a self-condensation reaction. Such behaviour can easily be explained by the high electrophilicity of the α,α-difluorocarbonyl group.

Conclusions

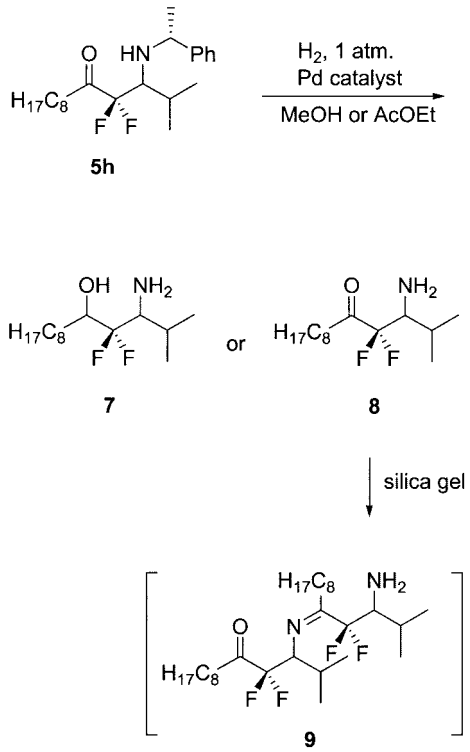
In summary, we have developed a convenient one-pot procedure for preparing various β-amino-α,α-difluoro ketones from acylsilanes, trifluoromethyltrimethylsilane and imines in very mild conditions. In an exploratory study, we have demonstrated that this strategy can be applied to a chiral series. Depending on the reaction conditions, palladium-catalyzed hydrogenation selectively afforded the 2,2-difluoro-1,3-amino alcohol or the unprotected β-amino-α,α-difluoro ketone.

Experimental Section

General Remarks: Melting points are uncorrected. Optical rotations were determined with a Perkin–Elmer Model 241 polarimeter. FTIR spectra were recorded with a MIDAC corporation apparatus. ^1H, ^{13}C and ^{19}F NMR spectra were recorded with a Bruker AC-250 spectrometer using $CDCl_3$ as the solvent. Tetramethylsilane was used as the internal standard for ^1H and ^{13}C NMR spectra and $CFCl_3$ for ^{19}F NMR spectra. MS data were obtained with a JEOL D300 apparatus at 70 eV in the electron-impact mode. Elemental analyses were performed with a Perkin–Elmer CHN 2400 apparatus. All reactions were monitored by TLC (Merck F 254) or GC. GC analyses were performed with a HP 6890 chromatograph equipped with a poly(dimethylsiloxane) HP ultra I column and a flame-ionization detector. Merck 9385 silica gel (40–63 μm) was used for flash chromatography. Commercially available reagents were used as supplied. Dichloromethane of puriss quality from Fluka (over molecular sieves) was used. Tetra-*n*-butylammonium difluorotriphenylstannate (DFTPS) was prepared according to the previously reported procedure.[22] The acylsilanes **1** and **2** were synthesized by the method developed by Corey[23] and Brook[24] and their co-workers. Imines **3c**,[25] **3d**,[26] **3e**,[27] **3f**,[11b,28,29] and oxazolidine **3i**[30] were prepared according to literature procedures.

(1*R*)-*N*-Isobutylidene-2-*tert*-butyldimethylsilyloxy-1-phenylethylamine (3j): Isobutyraldehyde (288 mg, 4 mmol) was added to a solution of (*R*)-2-*tert*-butyldimethylsilyloxy-1-phenylethylamine (1 g, 4 mmol) in CH_2Cl_2 (50 mL). The mixture was stirred for 12 h in the presence of $MgSO_4$ and then filtered. The solution was concentrated under reduced pressure to afford **3j** in a quantitative yield as a colourless oil. ^1H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 0.03 (s, 6 H, CH_3), 0.90 (s, 9 H, CH_3), 0.97 (d, $^3J_{HH}$ = 4.5 Hz, 3 H, 3′-H), 1.12 (d, $^3J_{HH}$ = 4.5 Hz, 3 H, 3′-H), 2.51 (dsept, $^3J_{HH}$ = 5.0, $^3J_{HH}$ = 4.5 Hz, 3 H, 2′-H), 3.78 (m, 2 H, 2-H), 4.15 (dd, $^3J_{HH}$ = 7.8, $^3J_{HH}$ = 5.2 Hz, 3 H, 1-H), 7.29–7.45 (m, 5 H, Ph), 7.63 (d, $^3J_{HH}$ = 5.0 Hz, 1 H, 1′-H) ppm. ^{13}C NMR (62.89 MHz, $CDCl_3$, 25 °C): δ = –4.9 (CH_3), 18.7 [$C(CH_3)_3$], 19.8 (C-3′), 19.9 (C-3′), 26.3 (CH_3), 34.5 (C-2′), 68.5 (C-2), 77.1 (C-1), 127.5 (Ph), 127.8 (Ph), 128.7

Table 4. Hydrogenolysis of imino aldol reaction product **5h**.



Entry	Catalyst	Solvent	Yield [%]	
			Amino alcohol **7**	Amino ketone **8**
1[a]	Pd/C 0.2 equiv.	MeOH	98[b]	–
2[a]	Pd/C 0.2 equiv.	AcOEt	92[c]	–
3[a]	$Pd(OH)_2$/C 0.2 equiv.	MeOH	53[d]	–
4[e]	$Pd(OH)_2$/C 0.2 equiv.	AcOEt	–	91[f]

[a] Reaction of a diastereomeric mixture of **5h**. [b] 48% *de*. [c] 50% *de*. [d] 62% *de*. [e] Reaction of the pure major diastereomer **5h**. [f] Yield of the crude product; silica gel chromatography gave isolated **8** (32%) and **9** (15%).

(Ph), 141.9 (Ph), 170.5 (C-1′) ppm. IR (film): $\tilde{\nu}$ = 2957, 2929, 2857, 1670, 1601, 1105 cm^{-1}.

Imino Aldol Reaction – General Procedure

In situ Preparation of the Difluoroenoxysilane: A catalytic amount of tetra-*n*-butylammonium difluorotriphenylstannate (54 mg, 0.08 mmol) was added to a solution of acylsilane **1** or **2** (1.5 mmol) and (trifluoromethyl)trimethylsilane (0.30 mL, 2.0 mmol) in dry CH_2Cl_2 (5 mL) at 0 °C under argon and protected from light. After stirring for 5 min at 0 °C, the reaction mixture was stirred for 25 min at room temperature. The formation of the difluoroenoxysilane was monitored by GC and was used in the next step in a one-pot procedure.

BF_3·OEt_2 Activation of the Imine: Imine **3** (1.8 mmol, 1.2 equiv.) and BF_3·OEt_2 (0.38 mL, 0.38 mmol, 2 equiv.) were added to the difluoroenoxysilane solution at –78 °C. The temperature was allowed to rise slowly to room temperature. After stirring overnight at room temperature, the reaction was quenched by addition of a saturated $NaHCO_3$ solution (10 mL). After extraction with CH_2Cl_2 (3 × 15 mL), the organic layer was washed with brine, dried with $MgSO_4$ and the solvent evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (see Table 1).

CF_3SO_3H Activation of the Imine: The difluoroenoxysilane solution was added to a solution of imine **3** (1.8 mmol, 1.2 equiv.) and triflic acid (1.65 mmol, 1.1 equiv.) under argon at 0 °C. After stirring for 45 min at room temperature, the reaction was quenched by addition of a saturated $NaHCO_3$ solution (10 mL). After extraction with CH_2Cl_2 (3 × 15 mL), the organic layer was washed with brine, dried with $MgSO_4$ and the solvent evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (see Table 1).

$Yb(OTf)_3$ or TMSOTf Activation of the Imine: Imine **3** (1.8 mmol, 1.2 equiv.) and $Yb(OTf)_3$ (0.15 mmol, 0.1 equiv.) at room temperature or TMSOTf (0.15 mmol, 0.1 equiv.) at 0 °C was added to the difluoroenoxysilane solution. The reaction mixture was stirred overnight [$Yb(OTf)_3$] or for 4 h (TMSOTf) at room temperature. A saturated $NaHCO_3$ solution (10 mL) was then added. After extraction with CH_2Cl_2 (3 × 15 mL), the organic layer was washed with brine, dried with $MgSO_4$ and the solvent evaporated under reduced pressure. The crude product was purified by column chromatography over silica gel (see Table 1).

3-Benzylamino-2,2-difluoro-1,3-diphenylpropan-1-one (4b): Procedure with BF_3·OEt_2. Elution: ethyl acetate/petroleum ether, 2:98. Pale yellow liquid (190 mg, 36%). ^1H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 2.18 (s, 1 H, NH), 3.52 (d, J_{AB} = 13.2 Hz, 1 H, CH_2), 3.79 (d, J_{AB} = 13.2 Hz, 1 H, CH_2), 4.44 (dd, $^3J_{HF}$ = 20.2, $^3J_{HF}$ = 7.6 Hz, 1 H, 3-H), 7.05–7.65 (m, 13 H, Ph), 7.99 (d, $^3J_{HH}$ = 7.6 Hz, 2 H, Ph) ppm. ^{13}C NMR (62.89 MHz, $CDCl_3$, 25 °C): δ = 50.8 (CH_2), 63.6 (t, $^2J_{CF}$ = 27.4 Hz, C-3), 117.8 (t, $^1J_{CF}$ = 257.9 Hz, C-2), 127.1, 128.2, 128.3, 128.6, 129.1, 129.7, 133.4, 133.8, 134.6, 138.9 (Ph), 190.4 (t, $^2J_{CF}$ = 28.6 Hz, C-1) ppm. ^{19}F NMR (235.36 MHz, $CDCl_3$, 25 °C): δ = –102.4 (dd, J_{AB} = 270.9, $^3J_{HF}$ = 7.6 Hz, 1 F), –115.3 (dd, J_{AB} = 270.9, $^3J_{HF}$ = 20.2 Hz, 1 F) ppm. IR (film): $\tilde{\nu}$ = 3355, 3063, 3021, 2916, 2853, 1705, 1597, 1454, 918 cm^{-1}. MS (EI): *m/z* (%) = 352 (6) $[M + 1]^+$, 260 (6), 239 (6), 226 (9), 211 (9), 197 (100), 178 (11), 165 (12), 156 (35), 140 (30), 127 (14), 117 (18), 105 (65). $C_{22}H_{19}ONF_2$: calcd. C 75.20, H 5.45, N 3.99; found C 75.08, H 5.80, N 3.55.

3-Benzylamino-2,2-difluoro-1-phenylpentan-1-one (4c): Procedure with BF_3·OEt_2. Elution: ethyl acetate/cyclohexane, 2:98. Pale yellow liquid (208 mg, 46%). ^1H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 1.02 (t, $^3J_{HH}$ = 7.6 Hz, 3 H, 5-H), 1.63 (quint., $^3J_{HH}$ = 7.6 Hz, 2 H, 4-H), 3.35 (ddt, $^3J_{HF}$ = 21.0, $^3J_{HF}$ = 8.0, $^3J_{HH}$ = 7.6 Hz, 1 H, 3-H), 2.10 (s, 1 H, NH), 3.42 (d, J_{AB} = 13.2 Hz, 1 H, 1′-H), 3.76 (d, J_{AB} = 13.2 Hz, 1 H, 1′-H), 7.25–7.47 (m, 8 H, Ph), 7.96 (d, $^3J_{HH}$ = 7.3 Hz, 2 H, Ph) ppm. ^{13}C NMR (62.89 MHz, $CDCl_3$, 25 °C): δ = 13.7 (C-5), 21.5 (C-4), 50.3 (C-1′), 66.4 (t, $^2J_{CF}$ = 25.9 Hz, C-3), 118.6 (t, $^1J_{CF}$ = 258.0 Hz, C-2), 128.4, 128.5, 129.0, 129.5, 129.7, 129.9, 133.6, 135.8 (Ph), 190.3 (t, $^2J_{CF}$ = 29.0 Hz, C-1) ppm. ^{19}F NMR (235.36 MHz, $CDCl_3$, 25 °C): δ = –104.1 (dd, J_{AB} = 267.0, $^3J_{HF}$ = 8.0 Hz, 1 F), –114.4 (dd, J_{AB} = 267.0, $^3J_{HF}$ = 21.0 Hz, 1 F) ppm. IR (film): $\tilde{\nu}$ = 3349, 3063, 3030, 2965, 2933, 1705, 1494, 1125 cm^{-1}.

Ethyl 2,2-Difluoro-3-oxo-1,3-diphenylpropylcarbamate (4d): Procedure with CF_3SO_3H. Elution: ethyl acetate/petroleum ether, 10:90. White solid (410 mg, 82%); m.p. 101 °C. ^1H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 1.22 (t, $^3J_{HH}$ = 7.1 Hz, 3 H, CH_3), 4.11 (q, $^3J_{HH}$ = 7.1 Hz, 2 H, CH_2), 5.63 (m, 2 H, NH, 1-H), 7.26–8.01 (m, 10 H, Ph) ppm. ^{13}C NMR (62.89 MHz, $CDCl_3$, 25 °C): δ = 14.3 (CH_3), 57.4 (t, $^2J_{CF}$ = 24.6 Hz, C-1), 61.5 (CH_2), 116.6 (t, $^1J_{CF}$ = 259.9 Hz, C-2), 128.3, 128.5, 128.6, 129.8, 132.2, 133.8,

134.4, 155.7 (Ph), 188.7 (t, $^2J_{CF}$ = 28.6 Hz, C-3) ppm. ^{19}F NMR (235.36 MHz, $CDCl_3$, 25 °C): δ = –106.7 (d, $^3J_{HF}$ = 11.4 Hz, 2 F) ppm. IR (film): $\tilde{\nu}$ = 3366, 2990, 1701, 1533, 1450, 1248, 1039 cm^{-1}. MS (EI): *m*/*z* (%) = 334 (27) [M + 1]$^+$, 313 (14), 240 (11), 178 (100), 140 (15), 105 (81). $C_{18}H_{17}O_3NF_2$: calcd. C 64.86, H 5.14, N 4.20; found C 64.80, H 4.93, N 4.16.

Ethyl 2,2-Difluoro-3-oxo-1-phenylundecylcarbamate (5d): Procedure with CF_3SO_3H. Elution: ethyl acetate/petroleum ether 5:95. Orange liquid (387 mg, 70%). ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 0.88 (t, $^3J_{HH}$ = 6.9 Hz, 3 H, CH_3), 1.10–1.40 (m, 13 H, 6-H, 7-H, 8-H, 9-H, 10-H, 11-H), 1.47 (quint., $^3J_{HH}$ = 7.2 Hz, 2 H, 5-H), 2.46 (t, $^3J_{HH}$ = 7.2 Hz, 2 H, 4-H), 4.11 (q, $^3J_{HH}$ = 6.9 Hz, 2 H, CH_2), 5.40 (m, 1 H, 1-H), 5.76 (d, $^3J_{HH}$ = 9.9 Hz, 1 H, NH), 7.35 (m, 5 H, Ph) ppm. ^{13}C NMR (62.89 MHz, $CDCl_3$, 25 °C): δ = 13.8 (CH_3), 14.2 (CH_3), 22.1, 22.4, 28.5, 28.8, 29.0, 31.4, 31.5 (C-10, C-9, C-8, C-7, C-6, C-5, C-4), 56.3 (t, $^2J_{CF}$ = 25.1 Hz, C-1), 61.4 (CH_2), 115.2 (t, $^1J_{CF}$ = 259.9 Hz, C-2), 128.2, 128.5, 128.6, 133.6 (Ph), 155.7 (CO), 200.9 (t, $^2J_{CF}$ = 28.5 Hz, C-3) ppm. ^{19}F NMR (235.36 MHz, $CDCl_3$, 25 °C): δ = –113.2 (dd, J_{AB} = 263.2, $^3J_{HF}$ = 11.4 Hz, 1 F), –115.1 (dd, J_{AB} = 263.2, $^3J_{HF}$ = 15.2 Hz, 1 F) ppm. IR (film): $\tilde{\nu}$ = 3314, 2917, 2853, 1705, 1529, 1462, 1404, 1244, 1036 cm^{-1}. MS (EI): *m*/*z* (%) = 370 (7) [M + 1]$^+$, 251 (7), 209 (9), 179 (100), 162 (10), 150 (16), 140 (12), 134 (46). $C_{20}H_{29}O_3NF_2$: calcd. C 65.02, H 7.91, N 3.79; found C 64.93, H 7.89, N 3.80.

***tert*-Butyl 2,2-Difluoro-3-oxo-1,3-diphenylpropylcarbamate (4e):** Procedure with $Yb(OTf)_3$. Elution: ethyl acetate/petroleum ether 5:95. White solid (239 mg, 44%), m.p. 141 °C. ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 1.41 (s, 9 H, CH_3), 5.45–5.70 (m, 2 H, NH, 1-H), 7.20–7.68 (m, 8 H, Ph), 8.01 (d, $^3J_{HH}$ = 8.0 Hz, 2 H, Ph) ppm. ^{13}C NMR (62.89 MHz, $CDCl_3$, 25 °C): δ = 28.2 (CH_3), 57.2 (t, $^2J_{CF}$ = 23.6 Hz, C-1), 80.5 [*C*(CH_3)$_3$], 116.8 (t, $^1J_{CF}$ = 259.9 Hz, C-2), 128.4, 128.6, 128.7, 129.9, 132.4, 134.0, 134.4 (Ph), 154.7 (CO), 188.9 (t, $^2J_{CF}$ = 28.5 Hz, C-3) ppm. ^{19}F NMR (235.36 MHz, $CDCl_3$, 25 °C): δ = –106.1 (dd, J_{AB} = 282.3, $^3J_{HF}$ = 7.6 Hz, 1 F), –108.1 (dd, J_{AB} = 282.3, $^3J_{HF}$ = 11.5 Hz, 1 F) ppm. IR (film): $\tilde{\nu}$ = 3375, 2978, 2351, 1705, 1692, 1529, 1253, 1178 cm^{-1}. MS (EI): *m*/*z* (%) = 362 (0.1) [M + 1]$^+$, 306 (7), 240 (16), 206 (100), 194 (10), 156 (25), 150 (35), 105 (13). $C_{20}H_{21}O_3NF_2$: calcd. C 66.47, H 5.86, N 3.88; found C 66.62, H 5.77, N 3.69.

***tert*-Butyl 2,2-Difluoro-3-oxo-1-phenylundecylcarbamate (5e):** Procedure with $Yb(OTf)_3$. Elution: ethyl acetate/petroleum ether 2:98. White solid (417 mg, 70%), m.p. 77 °C. ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 0.88 (t, $^3J_{HH}$ = 6.5 Hz, 3 H, 11-H), 1.22 (m, 10 H, 6-H, 7-H, 8-H, 9-H, 10-H), 1.42 (s, 9 H, CH_3), 1.56 (m, 2 H, 5-H), 2.49 (t, $^3J_{HH}$ = 6.9 Hz, 2 H, 4-H), 5.40 (m, 2 H, NH, 1-H), 7.36 (m, 5 H, Ph) ppm. ^{13}C NMR (62.89 MHz, $CDCl_3$, 25 °C): δ = 14.0 (C-11), 22.3, 22.6, 28.2, 28.7, 29.0, 29.1, 31.7, 37.6 (CH_3, C-10, C-9, C-8, C-7, C-6, C-5, C-4), 56.1 (t, $^2J_{CF}$ = 31.8 Hz, C-1), 80.6 [*C*(CH_3)$_3$], 115.4 (t, $^1J_{CF}$ = 259.8 Hz, C-2), 128.3, 128.7, 128.8, 133.8 (Ph), 154.7 (CO), 200.1 (t, $^2J_{CF}$ = 29.2 Hz, C-3) ppm. ^{19}F NMR (235.36 MHz, $CDCl_3$, 25 °C): δ = –113.0 (dd, J_{AB} = 263.2, $^3J_{HF}$ = 7.6 Hz, 1 F), –116.1 (dd, J_{AB} = 263.2, $^3J_{HF}$ = 15.3 Hz, 1 F) ppm. $C_{22}H_{33}O_3NF_2$: calcd. C 66.47, H 8.37, N 3.52; found C 66.48, H 8.31, N 3.20.

1,1-Difluoro-1-(*p*-tolylsulfinyl)decan-2-one (6): Procedure with $Yb(OTf)_3$ (0.4 equiv.). Elution: diethyl ether/petroleum ether, 4:96. Orange liquid (64 mg, 13%). ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 0.86 (t, $^3J_{HH}$ = 6.5 Hz, 3 H, 11-H), 1.25 (m, 10 H, 6-H, 7-H, 8-H, 9-H, 10-H), 1.52 (m, 2 H, 5-H), 2.44 (s, 3 H, CH_3), 2.58 (m, 2 H, 4-H), 7.37 (d, $^3J_{HH}$ = 8.0 Hz, 2 H, Ar), 7.56 (d, $^3J_{HH}$ = 8.0 Hz, 2 H, Ar) ppm. ^{13}C NMR (62.89 MHz, $CDCl_3$, 25 °C): δ = 14.1 (C-10), 21.7 (CH_3), 22.2, 22.7, 28.8, 29.1, 29.3, 31.8, 40.5 (C-9, C-8, C-7, C-6, C-5, C-4, C-3), 119.2 (dd, $^1J_{CF}$ = 308.1, $^1J_{CF}$ = 302.2 Hz, C-1), 125.9, 130.2, 136.6, 144.1 (Ar), 196.4 (t, $^2J_{CF}$ = 24.1 Hz, C-2) ppm. ^{19}F NMR (235.36 MHz, $CDCl_3$, 25 °C): δ = –110.0 (d, J_{AB} = 228.9 Hz, 1 F), –113.8 (d, J_{AB} = 228.9 Hz, 1 F) ppm. IR (film): $\tilde{\nu}$ = 2926, 2855, 1744, 1595, 1462, 1146 cm^{-1}.

(*S*$_S$)-2,2-Difluoro-1-phenyl-1-(*p*-tolylsulfinylamino)undecan-3-one (5f): Procedure with $Yb(OTf)_3$ (0.4 equiv.). Elution: diethyl ether/petroleum ether, 4:96. Orange oil (33 mg, 5%). ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 0.88 (t, $^3J_{HH}$ = 6.7 Hz, 3 H, 11-H), 1.25 (m, 10 H, 6-H, 7-H, 8-H, 9-H, 10-H), 1.55 (quint., $^3J_{HH}$ = 6.7 Hz, 2 H, 5-H), 2.43 (s, 3 H, CH_3), 2.58 (t, $^3J_{HH}$ = 6.7 Hz, 2 H, 4-H), 5.16 (dd, $^3J_{HF}$ = 16.4, $^3J_{HF}$ = 7.4 Hz, 1 H, 1-H), 7.13–7.60 (m, 5 H, Ph) ppm. ^{19}F NMR (235.36 MHz, $CDCl_3$, 25 °C): δ =– 113.7 (dd, J_{AB} = 270.8, $^3J_{HF}$ = 7.4 Hz, 1 F), –123.3 (dd, J_{AB} = 270.8, $^3J_{HF}$ = 16.4 Hz, 1 F) ppm. IR (film): $\tilde{\nu}$ = 2928, 2857, 1740, 1597, 1458, 1146, 812 cm^{-1}.

2,2-Difluoro-1,3-diphenyl-3-[(1*R*)-1-phenylethylamino]propan-1-one (4g): Procedure with $BF_3{\cdot}OEt_2$. Elution: diethyl ether/petroleum ether, 3:97 (290 mg, 53%). Major diastereomer (*R*,*R*): Yellow liquid. ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 1.18 (d, $^3J_{HH}$ = 6.5 Hz, 3 H, 2′-H), 2.18 (s, 1 H, NH), 3.78 (q, $^3J_{HH}$ = 6.5 Hz, 1 H, 1′-H), 4.68 (dd, $^3J_{HF}$ = 21.4, $^3J_{HF}$ = 6.9 Hz, 1 H, 3-H), 7.17–7.67 (m, 13 H, Ph), 8.14 (d, $^3J_{HH}$ = 7.3 Hz, 2 H, Ph) ppm. ^{13}C NMR (62.89 MHz, $CDCl_3$, 25 °C): δ = 21.8 (C-2′), 54.9 (C-1′), 61.9 (t, $^2J_{CF}$ = 23.6 Hz, C-3), 118.1 (t, $^1J_{CF}$ = 258.9 Hz, C-2), 126.6, 126.8, 127.2, 128.4, 128.7, 129.6, 129.9, 130.5, 131.0, 133.6, 134.9, 145.1 (Ph), 191.0 (t, $^2J_{CF}$ = 28.2 Hz, C-2) ppm. ^{19}F NMR (235.36 MHz, $CDCl_3$, 25 °C): δ = –101.4 (dd, J_{AB} = 267.0, $^3J_{HF}$ = 6.9 Hz, 1 F), –116.8 (dd, J_{AB} = 267.0, $^3J_{HF}$ = 21.4 Hz, 1 F) ppm. IR (film): $\tilde{\nu}$ = 3400, 2968, 2926, 1709, 1450, 1132 cm^{-1}. MS (EI): *m*/*z* (%) = 366 (7) [M + 1]$^+$, 350 (34), 240 (7), 210 (92), 194 (25), 156 (27), 140 (41), 120 (26). $C_{23}H_{21}ONF_2$: calcd. C 75.60, H 5.79, N 3.83; found C 75.79, H 5.71, N 3.74. Minor diastereomer (*S*,*R*): Yellow liquid. ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 1.18 (d, $^3J_{HH}$ = 6.5 Hz, 3 H, 2′-H), 2.18 (s, 1 H, NH), 3.55 (q, $^3J_{HH}$ = 6.5 Hz, 1 H, 1′-H), 4.18 (dd, $^3J_{HF}$ = 22.1, $^3J_{HF}$ = 6.9 Hz, 1 H, 3-H), 6.91–7.70 (m, 13 H, Ph), 8.01 (d, $^3J_{HH}$ = 7.2 Hz, 2 H, Ph) ppm. ^{19}F NMR (235.36 MHz, $CDCl_3$, 25 °C): δ = –101.7 (dd, J_{AB} = 267.0, $^3J_{HF}$ = 6.9 Hz, 1 F), –116.6 (dd, J_{AB} = 267.0, $^3J_{HF}$ = 22.1 Hz, 1 F) ppm.

2,2-Difluoro-1-phenyl-1-[(1*R*)-1-phenylethylamino]undecan-3-one (5g): Procedure with $BF_3{\cdot}OEt_2$. Elution: diethyl ether/petroleum ether, 2:98 (499 mg, 83%). Major diastereomer (*R*,*R*): Yellow liquid. ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 0.92 (t, $^3J_{HH}$ = 6.9 Hz, 3 H, 11-H), 1.10–1.45 (m, 13 H, 2′-H, 10-H, 9-H, 8-H, 7-H, 6-H), 1.50–1.80 (m, 2 H, 5-H), 1.97 (s, 1 H, NH), 2.50–2.85 (m, 2 H, 4-H), 3.70 (q, $^3J_{HH}$ = 6.5 Hz, 1 H, 1′-H), 4.40 (dd, $^3J_{HF}$ = 22.9, $^3J_{HF}$ = 7.6 Hz, 1 H, 1-H), 7.15–7.50 (m, 10 H, Ph) ppm. ^{13}C NMR (62.89 MHz, $CDCl_3$, 25 °C): δ = 14.2 (C-11), 21.8 (C-2′), 22.6, 22.7, 29.0, 29.2, 31.9, 38.4 (C-10, C-9, C-8, C-7, C-6, C-5), 55.0 (C-1′), 61.2 (dd, $^2J_{CF}$ = 27.6, $^2J_{CF}$ = 21.7 Hz, C-1), 117.0 (dd, $^1J_{CF}$ = 259.9, $^1J_{CF}$ = 256.0 Hz, C-2), 126.6, 127.4, 128.6, 134.8, 145.3 (Ph), 202.8 (dd, $^2J_{CF}$ = 32.5 Hz $^2J_{CF}$ = 25.6 Hz, C-3) ppm. ^{19}F NMR (235.36 MHz, $CDCl_3$, 25 °C): δ = –107.6 (dd, J_{AB} = 255.6, $^3J_{HF}$ = 7.6 Hz, 1 F), –124.5 (dd, J_{AB} = 255.6, $^3J_{HF}$ = 22.9 Hz, 1 F) ppm. IR (film): $\tilde{\nu}$ = 2928, 2859, 1742, 1455, 1130 cm^{-1}. MS (EI): *m*/*z* (%) = 402 (7) [M + 1]$^+$, 212 (5), 210 (20), 123 (10), 122 (100), 120 (40), 106 (24). $C_{25}H_{33}ONF_2$: calcd. C 74.78, H 8.28, N 3.49; found C 74.56, H 8.50, N 3.23. Minor diastereomer (*S*,*R*): Yellow liquid. ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 0.92 (t, $^3J_{HH}$ = 6.9 Hz, 3 H, 11-H), 1.10–1.45 (m, 13 H, 2′-H, 10-H, 9-H, 8-H, 7-H, 6-H), 1.50–1.80 (m, 2 H, 5-H), 1.97 (s, 1 H, NH), 2.50–2.85 (m, 2 H, 4-H), 3.52 (q, $^3J_{HH}$ = 6.5 Hz, 1

H, 1′-H), 3.89 (dd, $^3J_{HF}$ = 22.9, $^3J_{HF}$ = 7.6 Hz, 1 H, 1-H), 7.15–7.50 (m, 10 H, Ph) ppm. ^{19}F NMR (235.36 MHz, $CDCl_3$, 25 °C): δ = –108.3 (dd, J_{AB} = 255.6, $^3J_{HF}$ = 7.6 Hz, 1 F), –124.1 (dd, J_{AB} = 255.6, $^3J_{HF}$ = 22.9 Hz, 1 F) ppm.

4,4-Difluoro-2-methyl-3-[(1*R*)-1-phenylethylamino]tridecan-5-one (5h): Procedure with BF_3·OEt_2. Elution: diethyl ether/petroleum ether, 1:99 (303 mg, 55%). Major diastereomer: Yellow liquid. $[\alpha]_D^{20}$ = +0.8 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 0.80–1.00 (m, 9 H, 1-H, 2′-H, CH_3), 1.20–1.40 (m, 13 H, 13-H, 12-H, 11-H, 10-H, 9-H, 8-H), 1.47 (s, 1 H, NH), 1.66 (m, 2 H, 7-H), 1.88 (dsept, $^3J_{HH}$ = 6.9, $^3J_{HH}$ = 3.4 Hz, 1 H, 2-H), 2.5 (m, 2 H, 6-H), 3.06 (ddd, $^3J_{HF}$ = 19.5, $^3J_{HF}$ = 11.5, $^3J_{HH}$ = 3.4 Hz, 1 H, 3-H), 3.94 (q, $^3J_{HH}$ = 6.5 Hz, 1 H, 1′-H), 7.20–7.50 (m, 5 H, Ph) ppm. ^{13}C NMR (62.89 MHz, $CDCl_3$, 25 °C): δ = 14.0 (C-13), 17.3 (CH_3), 21.0 (CH_3), 22.6 (C-12), 23.4 (C-2′), 27.8 (C-11), 29.0 (C-10), 29.1 (C-9), 29.3 (C-8), 31.8 (C-7), 38.3 (C-6), 56.6 (C-1′), 60.1 (dd, $^2J_{CF}$ = 24.6, $^2J_{CF}$ = 20.7 Hz, C-3), 119.4 (t, $^1J_{CF}$ = 258.9 Hz, C-4), 127.0, 127.2, 128.4, 137.2 (Ph), 203.4 (dd, $^2J_{CF}$ = 31.5, $^2J_{CF}$ = 26.6 Hz, C-5) ppm. ^{19}F NMR (235.36 MHz, $CDCl_3$, 25 °C): δ = –108.9 (dd, J_{AB} = 255.6, $^3J_{HF}$ = 11.5 Hz, 1 F), –117.5 (dd, J_{AB} = 255.6, $^3J_{HF}$ = 19.5 Hz, 1 F) ppm. IR (film): $\tilde{\nu}$ = 2930, 2859, 1742, 1468, 1456, 1130, 1049 cm^{-1}. MS (EI): *m*/*z* (%) = 368 (31) $[M + 1]^+$, 328 (5), 246 (15), 176 (35), 123 (8), 122 (100), 120 (42). Minor diastereomer: ^{19}F NMR (235.36 MHz, $CDCl_3$, 25 °C): δ = –107.2 (dd, J_{AB} = 255.6, $^3J_{HF}$ = 7.6 Hz, 1 F), –122.2 (dd, J_{AB} = 255.6, $^3J_{HF}$ = 26.7 Hz, 1 F) ppm.

2,2-Difluoro-3-[(1*R*)-2-hydroxy-1-phenylethylamino]-4-methyl-1-phenylpentan-1-one (4i): Procedure with BF_3·OEt_2. Elution: ethyl acetate/cyclohexane, 20:80 (320 mg, 63%). Major diastereomer: Yellow liquid. ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 0.78 (d, $^3J_{HH}$ = 6.9 Hz, 3 H, 5-H), 0.91 (d, $^3J_{HH}$ = 6.9 Hz, 3 H, 5-H), 1.85 (dsept, $^3J_{HH}$ = 6.9, $^3J_{HH}$ = 2.9 Hz 1 H, 4-H), 2.22 (m, 2 H, NH, OH), 3.28 (td, $^3J_{HF}$ = 15.0, $^3J_{HH}$ = 2.9 Hz 1 H, 3-H), 3.53 (m, 2 H, 2′-H), 4.01 (m, 1 H, 1′-H), 7.24–7.44 (m, 8 H, Ph), 7.98 (d, $^3J_{HH}$ = 6.5 Hz, 2 H, Ph) ppm. ^{13}C NMR (62.89 MHz, $CDCl_3$, 25 °C): δ = 16.7 (C-5), 20.7 (C-5), 28.3 (C-4), 61.2 (t, $^2J_{CF}$ = 20.6 Hz, C-3), 63.4 (C-1′), 67.1 (C-2′), 120.7 (t, $^1J_{CF}$ = 258.0 Hz, C-2), 126.9, 127.4, 127.8, 128.4, 128.5, 132.8, 134.1, 140.4 (Ph), 190.9 (t, $^2J_{CF}$ = 28.5 Hz, C-1) ppm. ^{19}F NMR (235.36 MHz, $CDCl_3$, 25 °C): δ = –104.9 (dd, J_{AB} = 270, $^3J_{HF}$ = 15 Hz, 1 F), –106.5 (dd, J_{AB} = 270, $^3J_{HF}$ = 15 Hz, 1 F) ppm. IR (film): $\tilde{\nu}$ = 3364, 2966, 2879, 1765, 1449, 1107 cm^{-1}. MS (EI): *m*/*z* (%) = 316 (47) $[M - 31]^+$, 176 (25), 105 (100), 91 (23), 77 (35). Minor diastereomer (as a mixture of two cyclic hemiacetals, selected data): ^{19}F NMR (235.36 MHz, $CDCl_3$, 25 °C): δ = –101.2 (dd, J_{AB} = 250, $^3J_{HF}$ = 13 Hz, 1 F), –102.8 (dd, J_{AB} = 266, $^3J_{HF}$ = 9 Hz, 1 F), –111.9 (dd, J_{AB} = 266, $^3J_{HF}$ = 20 Hz, 1 F), –121.1 (dd, J_{AB} = 250, $^3J_{HF}$ = 20 Hz, 1 F) ppm.

4,4-Difluoro-3-[(1*R*)-2-hydroxy-1-phenylethylamino]-2-methyltridecan-5-one (5i): Procedure with BF_3·OEt_2. Elution: ethyl acetate/cyclohexane, 10:90 (420 mg, 73%). Major diastereomer: Yellow liquid. ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 0.81 (d, $^3J_{HH}$ = 6.9 Hz, 3 H, 1-H), 0.83–0.89 (m, 6 H, 13-H, CH_3), 1.06–1.40 (m, 12 H, 12-H, 11-H, 10-H, 9-H, 8-H, 7-H), 1.42 (m, 2 H, NH, OH), 1.66 (m, 2 H, 6-H), 1.82 (m, 1 H, 2-H), 2.67 (t, $^3J_{HH}$ = 7.1 Hz, 1 H, 2′-H), 3.10 (m, 1 H, 3-H), 3.58 (t, $^3J_{HH}$ = 7.1 Hz, 1 H, 2′-H), 3.92 (t, $^3J_{HH}$ = 7.1 Hz, 1 H, 1′-H), 7.24–7.27 (m, 5 H, Ph) ppm. ^{13}C NMR (62.89 MHz, $CDCl_3$, 25 °C): δ = 14.0 (C-13), 28.4 (CH_3), 28.5 (CH_3), 29.3 (C-2), 29.5 (C-12), 29.7 (C-11), 29.8 (C-10), 29.9 (C-9), 31.7 (C-8), 31.8 (C-7), 37.9 (C-6), 60.5 (t, $^2J_{CF}$ = 22.8 Hz, C-3), 64.1 (C-1′), 67.6 (C-2′), 119.1 (t, $^1J_{CF}$ = 258.5 Hz, C-4), 126.9, 127.9, 128.5, 140.6 (Ph), 203.5 (dd, $^2J_{CF}$ = 31.9 Hz $^2J_{CF}$ = 28.1 Hz, C-5) ppm. ^{19}F NMR (235.36 MHz, $CDCl_3$, 25 °C): δ = –109.6 (dd, J_{AB} = 266, $^3J_{HF}$ = 12 Hz, 1 F), –114.3 (dd, J_{AB} = 266, $^3J_{HF}$ = 17 Hz, 1 F) ppm. IR (film): $\tilde{\nu}$ = 3450, 2928, 2854, 1738, 1455, 1111, 1038 cm^{-1}. Minor diastereomer (as a cyclic hemiacetal): ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 0.83–0.89 (m, 3 H, 13-H), 0.97 (d, $^3J_{HH}$ = 7.3 Hz, 3 H, 1-H), 1.05 (d, $^3J_{HH}$ = 6.6 Hz, 3 H, CH_3), 1.06–1.40 (m, 12 H, 12-H, 11-H, 10-H, 9-H, 8-H, 7-H), 1.42 (s, 2 H, NH, OH), 1.66 (m, 2 H, 6-H), 1.82 (m, 1 H, 2-H), 3.10 (m, 1 H, 3-H), 3.60 (dd, $^3J_{HH}$ = 11.1, $^3J_{HH}$ = 4 Hz, 1 H, 2′-H), 3.75 (dd, $^3J_{HH}$ = 12.3, $^3J_{HH}$ = 4 Hz, 1 H, 2′-H), 4.12 (dd, $^3J_{HH}$ = 12.3, $^3J_{HH}$ = 11.1 Hz, 1 H, 1′-H), 7.24–7.37 (m, 5 H, Ph) ppm. ^{13}C NMR (62.89 MHz, $CDCl_3$, 25 °C): δ = 14.5 (C-13), 28.4 (CH_3), 28.5 (CH_3), 28.6 (C-2), 29.6 (C-12), 29.7 (C-11), 29.8 (C-10), 29.9 (C-9), 31.7 (C-8), 33.5 (C-7), 37.9 (C-6), 68.0 (C-1′), 68.7 (C-2′), 71.2 (dd, $^2J_{CF}$ = 34.0, $^2J_{CF}$ = 24.5 Hz, C-3), 100.6 (t, $^2J_{CF}$ = 28.3 Hz, C-5), 121.1 (t, $^1J_{CF}$ = 258.5 Hz, C-4), 127.7, 128.5, 129.0, 138.7 (Ph) ppm. ^{19}F NMR (235.36 MHz, $CDCl_3$, 25 °C): δ = –107.6 (dd, J_{AB} = 246, $^3J_{HF}$ = 10 Hz, 1 F), –122.2 (dd, J_{AB} = 246, $^3J_{HF}$ = 20 Hz, 1 F) ppm.

3-[(1*R*)-2-*tert*-Butyldimethylsilyloxy-1-phenylethylamino]-2,2-difluoro-4-methyl-1-phenylpentan-1-one (4j): Procedure with BF_3·OEt_2. Elution: ethyl acetate/cyclohexane, 2:98 (372 mg, 54%). Major diastereomer: Yellow liquid. ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 0.07 (s, 6 H, CH_3), 0.92 (s, 9 H, CH_3), 1.11 (d, $^3J_{HH}$ = 4.5 Hz, 3 H, 5-H), 1.12 (d, $^3J_{HH}$ = 4.5 Hz, 3 H, 5-H), 1.70 (dsept, $^3J_{HH}$ = 4.5, $^3J_{HH}$ = 2.9 Hz 1 H, 4-H), 2.50 (m, 1 H, NH), 3.23 (ddd, $^3J_{HF}$ = 18.0, $^3J_{HF}$ = 12.0, $^3J_{HH}$ = 2.9 Hz 1 H, 3-H), 3.59 (m, 2 H, 2′-H), 4.29 (dd, $^3J_{HH}$ = 6.5, $^3J_{HH}$ = 4.5 Hz, 1 H, 1′-H), 7.24–7.47 (m, 8 H, Ph), 8.00 (d, $^3J_{HH}$ = 6.5 Hz, 2 H, Ph) ppm. ^{13}C NMR (62.89 MHz, $CDCl_3$, 25 °C): δ = –5.40 (CH_3), 16.3 (C-3′), 19.8 (C-3′), 18.1 [$C(CH_3)_3$], 21.8 (CH_3), 28.6 (C-4), 60,61 (t, $^2J_{CF}$ = 19.0 Hz, C-3), 62.9 (C-1′), 68.3 (C-2′), 121.1 (t, $^1J_{CF}$ = 257.0 Hz, C-2), 128.2 (Ph), 128.5 (Ph), 128.6 (Ph), 141.9 (Ph), 190.4 (t, $^2J_{CF}$ = 31.9 Hz $^2J_{CF}$ = 29.8 Hz, C-1) ppm. ^{19}F NMR (235.36 MHz, $CDCl_3$, 25 °C): δ = –100.1 (dd, J_{AB} = 268, $^3J_{HF}$ = 12 Hz, 1 F), –109.5 (dd, J_{AB} = 268, $^3J_{HF}$ = 18 Hz, 1 F) ppm. IR (film): $\tilde{\nu}$ = 3066, 2954, 2928, 1703, 1467, 1254 cm^1. Minor diastereomer (selected data): ^{19}F NMR (235.36 MHz, $CDCl_3$, 25 °C): δ = –100.2 (dd, J_{AB} = 261, $^3J_{HF}$ = 6 Hz, 1 F), –115.8 (dd, J_{AB} = 261, $^3J_{HF}$ = 24 Hz, 1 F) ppm.

Hydrogenolysis of 5h: A solution of **5h** (368 mg, 1 mmol, diastereomeric mixture) in MeOH (10 mL) was stirred under hydrogen in the presence of $Pd(OH)_2$/C (280 mg, 0.2 mmol) (or Pd/C, 0.2 equiv.). The reaction was monitored by GC and the reaction mixture was filtered through Celite. The solvent was evaporated under reduced pressure and the crude product was purified by column chromatography over silica gel (elution: diethyl ether/petroleum ether, 50:50) to give the amino alcohol **7** (141 mg, 53%) as a 81:19 mixture of two diastereomers.

3-Amino-4,4-difluoro-2-methyltridecan-5-ol (7): Major diastereomer: Yellow liquid. ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 0.86 (t, $^3J_{HH}$ = 6.9 Hz, 3 H, 13-H), 0.96 (d, $^3J_{HH}$ = 6.9 Hz, 3 H, 1-H), 0.98 (d, $^3J_{HH}$ = 6.9 Hz, 3 H, CH_3), 1.15-1.45 (m, 13 H, 12-H, 11-H, 10-H, 9-H, 8-H, 7-H, OH), 1.55-1.70 (m, 2 H, 6-H), 2.09 (dsept, $^3J_{HH}$ = 6.9, $^3J_{HH}$ = 2.7 Hz, 1 H, 2-H), 2.50–2.90 (m, 2 H, NH_2), 3.04 (dt, $^3J_{HF}$ = 22.9, $^3J_{HH}$ = 5.0 Hz, 1 H, 3-H), 3.70–3.95 (m, 1 H, 5-H) ppm. ^{13}C NMR (62.89 MHz, $CDCl_3$, 25 °C): δ = 14.0 (C-13), 16.9 (CH_3), 20.8 (CH_3), 22.6 (C-12), 25.7 (C-2), 29.2 (C-11), 29.4 (C-10), 29.5 (C-9), 30.7 (C-8), 30.8 (C-7), 31.8 (C-6), 57.6 (dd, $^2J_{CF}$ = 27.6, $^2J_{CF}$ = 24.6 Hz, C-3), 72.9 (t, $^2J_{CF}$ = 28.5 Hz, C-5), 122.8 (t, $^1J_{CF}$ = 251.0 Hz, C-4) ppm. ^{19}F NMR (235.36 MHz, $CDCl_3$, 25 °C): δ = –116.4 (dd, J_{AB} = 263.2, $^3J_{HF}$ = 15.3 Hz, 1 F), –118.7 (dd, J_{AB} = 263.2, $^3J_{HF}$ = 22.9 Hz, 1 F) ppm. IR (film): $\tilde{\nu}$ = 3378, 3310, 2924, 2857, 1736, 1595, 1468, 1082 cm^{-1}. MS (EI):

m/z (%) = 266 (17) $[M + 1]^+$, 100 (26), 88 (31), 74 (40), 72 (100). Minor diastereomer (selected data): ^{13}C NMR: δ = 59.6 (dd, $^2J_{CF}$ = 23.6, $^2J_{CF}$ = 28.6 Hz), 74.3 (dd, $^2J_{CF}$ = 30.5, $^2J_{CF}$ = 25.6 Hz), 122.8 (t, $^1J_{CF}$ = 251.0 Hz) ppm. ^{19}F NMR: δ = –131.4 (dt, J_{AB} = 255.6, $^3J_{HF}$ = 22.9 Hz, 1 F), –115.1 (d, J_{AB} = 255.6 Hz, 1 F) ppm.

The same procedure as above but in anhydrous EtOAc and with pure major diastereomer **5h** (368 mg, 1 mmol) in the presence of $Pd(OH)_2/C$ (280 mg, 0.2 mmol) gave **8** (239 mg, 91%). Purification by column chromatography over silica gel (elution: diethyl ether/petroleum ether, 15:85) gave pure amino ketone **8** (84 mg, 32%) and **9** (76 mg, 15%).

3-Amino-4,4-difluoro-2-methyltridecan-5-one (8): Colorless liquid. ^1H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 0.87 (t, $^3J_{HH}$ = 6.5 Hz, 3 H, 13-H), 0.93 (d, $^3J_{HH}$ = 6.9 Hz, 3 H, 1-H), 1.00 (d, $^3J_{HH}$ = 6.9 Hz, 3 H, CH_3), 1.13–1.43 (m, 12 H, 12-H, 11-H, 10-H, 9-H, 8-H, NH_2), 1.61 (quint., $^3J_{HH}$ = 6.9 Hz, 2 H, 7-H), 1.96 (dsept, $^3J_{HH}$ = 6.9, $^3J_{HH}$ = 3.1 Hz, 1 H, 2-H), 2.67 (t, $^3J_{HH}$ = 6.9 Hz, 2 H, 6-H), 3.11 (ddd, $^3J_{HF}$ = 20.6, $^3J_{HF}$ = 11.4, $^3J_{HH}$ = 3.1 Hz, 1 H, 3-H) ppm. ^{13}C NMR (62.89 MHz, $CDCl_3$, 25 °C): δ = 14.0 (C-13), 16.4 (CH_3), 20.8 (CH_3), 22.6 (C-2), 27.6 (C-12), 28.8 (C-11), 28.9 (C-10), 29.0 (C-9), 29.1 (C-8), 31.7 (C-7), 37.7 (C-6), 57.1 (dd, $^2J_{CF}$ = 24.6, $^2J_{CF}$ = 21.7 Hz, C-3), 118.1 (t, $^1J_{CF}$ = 256.9 Hz, C-4), 202.8 (dd, $^2J_{CF}$ = 32.5, $^2J_{CF}$ = 28.5 Hz, C-5) ppm. ^{19}F NMR (235.36 MHz, $CDCl_3$, 25 °C): δ = –112.7 (dd, J_{AB} = 267.0, $^3J_{HF}$ = 11.4 Hz, 1 F), –120.4 (dd, J_{AB} = 267.0, $^3J_{HF}$ = 20.6 Hz, 1 F) ppm. IR (film): $\tilde{\nu}$ = 3418, 2928, 2859, 1742, 1740, 1373, 1217, 1047 cm^{-1}. MS (EI): *m/z* (%) = 264 (11) $[M + 1]^+$, 74 (30), 72 (100).

3-[1-(2-Amino-1,1-difluoro-3-methylbutyl)nonylideneamino]-4,4-difluoro-2-methyltridecan-5-one (9): Colourless liquid. ^1H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 0.87 (t, $^3J_{HH}$ = 6.9 Hz, 6 H, 2 CH_3), 0.94 (d, $^3J_{HH}$ = 6.9 Hz, 6 H, 2 CH_3), 1.01 (d, $^3J_{HH}$ = 6.9 Hz, 6 H, 2 CH_3), 1.15–1.42 (m, 22 H, 10 CH_2, NH_2), 1.45–1.65 (m, 4 H, 2 CH_2), 1.95–2.25 [m, 2 H, 2 C*H*(CH_3)$_2$], 2.25–2.45 (m, 2 H CH_2CN), 2.50–2.75 (m, 2 H CH_2CO), 3.26 (ddd, $^3J_{HF}$ = 19.7, $^3J_{HF}$ = 11.4, $^3J_{HH}$ = 3.1 Hz, 1 H, CHN), 3.85–4.00 (m, 1 H, $CHNH_2$) ppm. ^{13}C NMR (62.89 MHz, $CDCl_3$, 25 °C): δ = 14.0–38.2 [22 C, 6 CH_3, 14 CH_2, 2 *C*H(CH_3)$_2$], 59.9 (dd, $^2J_{CF}$ = 27.6, $^2J_{CF}$ = 24.6 Hz, $CHNH_2$), 66.7 (t, $^2J_{CF}$ = 22.6 Hz, $CHNH_2$),118.1 (t, $^1J_{CF}$ = 256.9 Hz, CF_2), 121.0 (t, $^1J_{CF}$ = 251.0 Hz, CF_2), 172.1 (dd, $^2J_{CF}$ = 30.5, $^2J_{CF}$ = 28.5 Hz, CN), 202.2 (t, $^2J_{CF}$ = 29.5 Hz, CO) ppm. ^{19}F NMR (235.36 MHz, $CDCl_3$, 25 °C): δ = –107.8 (dd, J_{AB} = 270.9, $^3J_{HF}$ = 11.4 Hz, 1 F), –109.6 (dd, J_{AB} = 263.2, $^3J_{HF}$ = 11.4 Hz, 1 F), –111.5 (dd, J_{AB} = 270.9, $^3J_{HF}$ = 19.7 Hz, 1 F), –113.4 (dd, J_{AB} = 263.2, $^3J_{HF}$ = 15.3 Hz, 1 F) ppm. IR (film): $\tilde{\nu}$ = 2928, 2857, 1477, 1672, 1468, 1372, 1039 cm^{-1}.

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