Generation and Use of an Equivalent of Difluoroacetamide or Difluoroacetate Anions**

Gaëlle Blond, Thierry Billard,* and Bernard R. Langlois*[a]

Dedicated to Professor Dieter Naumann on the occasion of his 60th birthday

Abstract: Ethers of trifluoroacetaldehyde hemiaminals can undergo dehydrofluorination under basic conditions to provide ethers of difluoroketene hemiaminals. The latter behave as equivalents of difluoroacetamide or difluoroacetate anions towards various electrophiles, yielding a range of difluoromethylcarbonyl products.

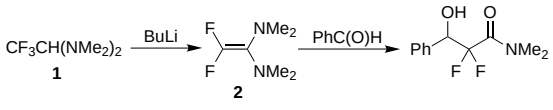
Keywords: hemiaminals · nucleophilic addition · nucleophilic substitution · synthetic methods

Introduction

Because of the particular properties of fluorine, the introduction of such an element on organic substrates induces dramatic consequences on their chemical and biological activities.[1] Among fluorinated compounds, difluoromethylated ones present unique biological properties.[2] For this reason, a variety of methods have been developed for their preparation.[3]

Among them, the introduction of difluoromethylcarbonyl moieties, which can be functionalized in further steps, constitutes an attractive strategy. For example, Reformatsky-type reactions with halodifluoroacetates are often used for this purpose[3a, 4] but are limited by lack of availability of such reagents. Selective defluorination of a trifluoromethyl group is another fruitful strategy and has been widely studied. Especially, Portella et al. have shown that difluoroenoxysilanes, generated from acylsilanes and Ruppert's reagent (CF_3SiMe_3), constitute equivalents of the difluoromethylcarbonyl anion.[5] Nevertheless, CF_3SiMe_3 is difficult to use on a larger scale. On the other hand, Uneyama et al. have reported on the electroreductive defluorination of trifluoromethyl ketones[6] or trifluoroacetic acid esters,[7] in the presence of trimethylsilyl chloride, which provides α,α-difluoroenol silyl ethers or α,α-difluoroketenes silyl acetals, respectively. These intermediates can behave, under fluoride activation, as difluoromethylene anions but their preparation needs specific electrochemical conditions. The same authors have also demonstrated that magnesium can be used to promote reductive defluorination. The resulting α-silyl difluoroacetates can react in the same way as the Ruppert's reagent.[8] However, the required excess of magnesium constitutes an environmental drawback.

Finally, Dolbier et al. achieved the basic dehydrofluorination of 1,1-bis(dialkylamino)-2,2,2-trifluorethanes **1** to generate difluoroketenes aminals **2** which, after reaction with benzaldehydes, provided β-hydroxy-α,α-difluoropropionamides (Scheme 1).[9] Although this strategy is very elegant, the access to **1** is not easy and limits its synthetic applications.



Scheme 1. Synthesis of α,α-difluoropropionamides from Dolbier's reagent.

During our investigations on the potentials of this new family of fluorinated hemiaminals we are currently developing,[10, 11] we examined the use of such compounds as difluoromethylenecarboxyl building blocks.

Results and Discussion

Our first goal was to deprotonate the silylated hemiaminal **3** to obtain, after loss of fluoride, the silylated difluoroketene hemiaminal **4** (Scheme 2).

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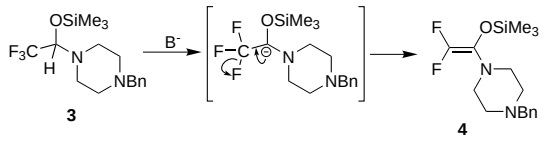
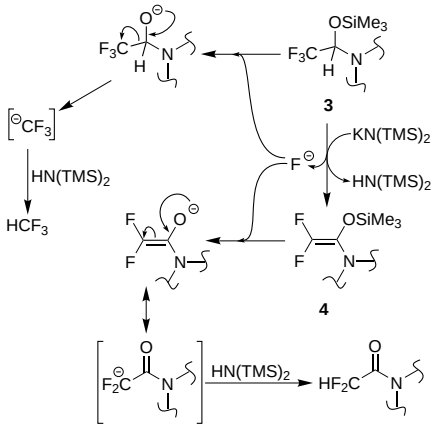


Scheme 2. Deprotonation of the silylated hemiaminal **3**.

Different basic systems have been tested to generate **4**. It appeared that hydrides and alcoholates were not strong enough to deprotonate **3**. Also, lithiated amides (LDA or LiHMDS), even complexed by TMEDA, were not dissociated enough to be efficient. Surprisingly, silicophilic attack occured with butyl lithium, instead of the expected deprotonation. Finally, deprotonation succeeded with $KN(SiMe_3)_2$ but the fluoride anions, arising from a subsequent β-elimination, desilylated **4** and **3** (which then lose $^{-}CF_3$).[10a] The anions thus formed were protonated by $HN(TMS)_2$, generated in situ, to provide fluoroform and difluoroacetamide (Scheme 3).

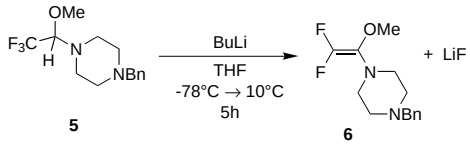


Scheme 3. Reaction of **3** with $KN(TMS)_2$.

Since a silyl group seemed prejudicial for this reaction, we then turned our attention to the methylated hemiaminal derivative **5** that we previously described[11] and which is easily synthesized from **3**.[11b]

A rapid study of the deprotonation conditions showed that $KN(TMS)_2$ could not deprotonate **5**, probably because of the less acidic character of the proton, compared with that in **3**.[12] On the contrary, BuLi was able to abstract the hydrogen in α-position to the CF_3 group. A more accurate study of the reaction conditions underlined the limited stability of the resulting ketene hemiaminal **6** at room temperature. Finally, the optimal results, compatible with a reasonable kinetics, were obtained when slowly warming, for five hours, the reaction medium from -78 to $10\,^{\circ}C$ (Scheme 4).

Abstract in French: *Les éthers d'hémiaminals du trifluoroacétaldéhyde subissent, en milieu basique, une déshydrofluoration pour conduire à des éthers d'hémiaminals de difluorocétènes. Ces derniers peuvent alors réagir comme des équivalents d'anions de dérivés de l'acide difluoroacétique envers divers électrophiles pour fournir des composés difluorométhylés variés.*

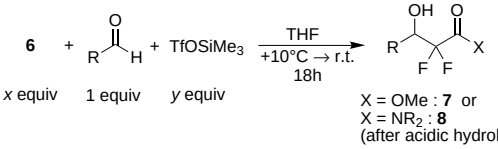


Scheme 4. Deprotonation of the methylated hemiaminal **5**.

As **6** could not be isolated, its reactivity towards aldehydes was studied in situ (Table 1).

Notably, **6** reacted very easily with benzaldehyde to yield, after acidic hydrolysis, the expected compound **7a** (entry 1). Nevertheless, 2-naphtaldehyde delivered a disappointing result under the same conditions (entry 4). To improve this reaction, we ventured the hypothesis that the fluoride anions, present in the reaction mixture, could be harmful. Thus, they were quenched by trimethylsilyl triflate ($TfOSiMe_3$) before introducing the aldehyde. Thus, the yield of **7b** increased (entry 5) and was optimized with two equivalents of **6** and $TfOSiMe_3$ (entry 6). Surprisingly, when applied to benzaldehyde, these optimal conditions led to worse results (entries 2, 3).

Table 1. Reactivity of **6** with aldehydes.



Entry	RCHO	**6** (*x* equiv)	$TfOSiMe_3$ (*y* equiv)	**7** (%)[a]	**8** (%)[a]
1	benzaldehyde	1	0	**7a**: (80) 75	
2	benzaldehyde	1	1	**7a**: (40)	
3	benzaldehyde	2	2	**7a**: (45)	
4	2-naphthaldehyde	1	0	**7b**: (36)	
5	2-naphthaldehyde	1	1	**7b**: (62)	
6	2-naphthaldehyde	2	2	**7b**: (70) 60	
7	valeraldehyde	2	2	**7c**: 50	**8c**: 20
8	(6-methoxy)-2-naphthaldehyde	2	0	**7d**: (20)	
9	(6-methoxy)-2-naphthaldehyde	2	2	**7d**: 65	**8d**: 25
10	octanaldehyde	2	2	**7e**: 70	**8e**: 25
11	3-formylthiophene	2	2	**7f**: 64	**8f**: 22
12	cinnamaldehyde	2	2	**7g**: 55	**8g**: 35
13	*N*-Boc-3-formylindole	2	2	**7h**: 80	**8h**: 10

[a] Isolated yield. In parentheses: crude yields determined by ^{19}F NMR with internal standard ($PhOCF_3$).

Nevertheless, despite these two opposite results, the procedure using $TfOSiMe_3$ was applied to other aldehydes since benzaldehyde, which is well known to be very reactive, could constitute an exception (Table 1). Generally, good yields were reached. In contrast to Dolbier's reagent **2**,[9] **6** reacted also with enolizable aldehydes to deliver the corresponding carbinols (entries 7, 10). However, a mixture of ;ester **7** (major product) and amide **8** (in around 20% yield) was usually obtained. These two compounds arised from the hydrolysis of the resonance forms of the adduct resulting from the nucleophilic attack of **6** on the aldehyde substrate (Scheme 5).

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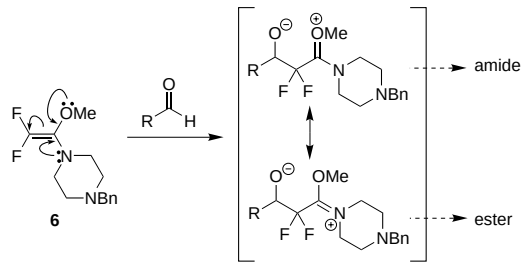
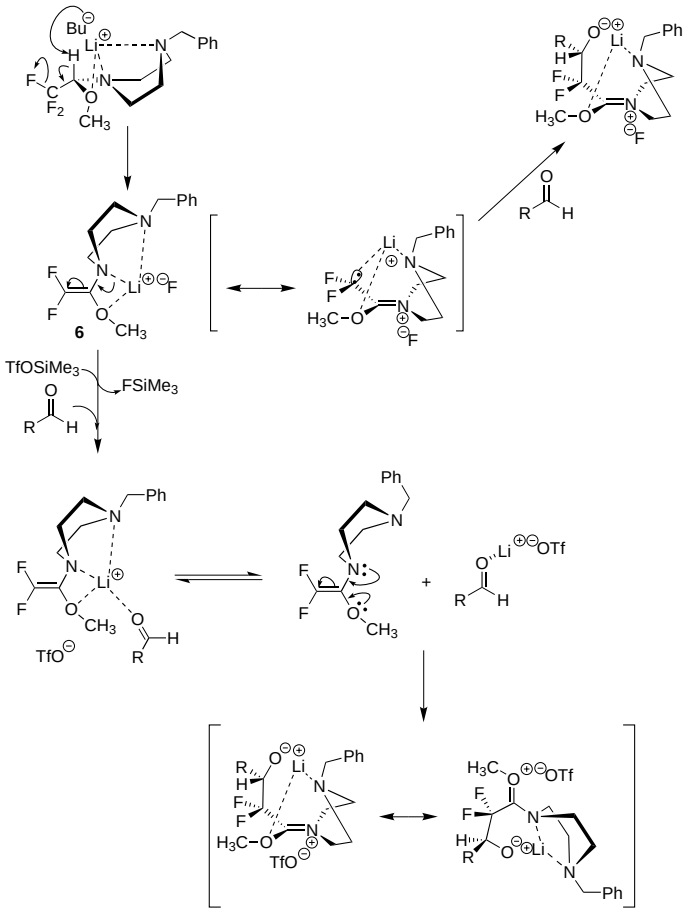


Scheme 5. Synthesis of esters or amides from **6**.

The fact that this phenomenon occured only when TfOSiMe$_3$ was added (entries 8, 9) and that this additive increased the overall yield of products led us to propose the mechanism shown in Scheme 6.



Scheme 6. Mechanism of reaction of **6** with aldehydes.

After deprotonation of **5**, the lithium fluoride generated forms a rather tight ion pair in which lithium interacts with both the nitrogen and the oxygen atoms of **6**. When no trimethylsilyl triflate was added, the iminium formation is only favored because the strong chelation of lithium cation by the oxygen doublets prevents their conjugation with the π system. Thus, only the ester is obtained after hydrolysis.

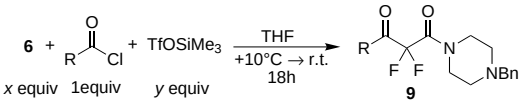
When TfOSiMe$_3$ is added, lithium triflate is formed as a loose ion pair and, because of its mild Lewis acid character,[13] activates the aldehyde. Consequently, nitrogen and oxygen atoms of **6** are no longer chelated by lithium and both iminium or oxonium forms can be considered. After reaction with aldehyde and hydrolysis, they lead to ester **7** and amide **8**, respectively. Nevertheless, because of a better overlap of the orbitals of nitrogen doublets with π electrons,[14] a higher weight can be attributed to the iminium resonance form and, consequently, the ester is the major product.

The case of naphthaldehyde, from which no amide was formed even in the presence of TfOSiMe$_3$, can be interpreted by the fact that this aldehyde is reactive enough that it doesn't need any activation. Thus, the rapid process without activation matched the one with TfOSiMe$_3$ activation so that the amount of amide formed was too low to be either detected or isolated.

In contrast, simple ketones such as benzophenone, chalcone or acetophenone were not reactive enough to undergo nucleophilic attack from **6**, even with Lewis acid activation ($BF_3 \cdot Et_2O$, Bu_2BOTf, TfOSiMe$_3$, …), whereas activated ketones, such as α-ketoesters, did react (see Table 3, entry 2).

Since very reactive substrates were needed, our interest was then focused on acyl chlorides (Table 2).

Table 2. Reaction of **6** with acyl chlorides.



Entry	R	*x* (equiv)	*y* (equiv)	**9** (%)[a]
1	Ph	1	0	**9a**: 25 (35)
2	Ph	1	1	**9a**: (50)
3	Ph	2	2	**9a**: 70 (80)
4	cyclopropyl	2	2	**9b**: 57 (60)
5	*tert*-butyl	2	2	0
6	Ph_2N	2	2	0

[a] Isolated yield. In parentheses crude yield determined by ^{19}F NMR with internal standard ($PhOCF_3$).

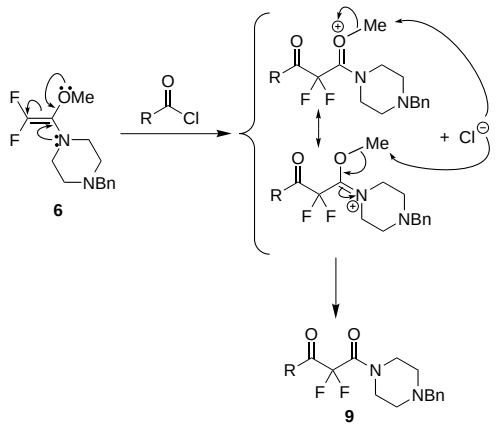
In this case, fluoride anions must always be quenched (entries 1, 2); otherwise, acyl fluorides, which are generally less reactive than chlorides, were formed.[15] This hypothesis was verified by the absence of any reaction between benzoyl fluoride and **6**. As for aldehydes, the best results were obtained with two equivalents of **6** and TfOSiMe$_3$ (entry 3) but, in contrast to aldehydes, amides **9** were exclusively formed.

This result can be explained by a subsequent Krapcho-type reaction from the chloride anions liberated in the medium (Scheme 7).

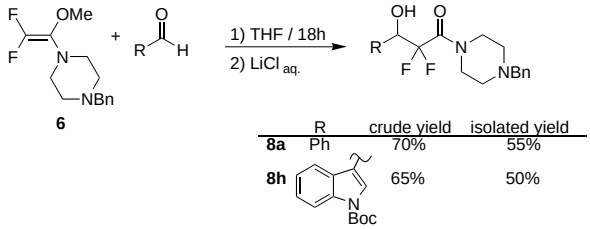
This hypothesis has been confirmed by hydrolyzing the crude mixture resulting from **6** and benzaldehyde, with a aqueous saturated LiCl solution: Amide **8a** was exclusively obtained instead of ester **7a**. The same result was observed from *N*-Boc-3-formylindole which delivered amide **8h** (Scheme 8).

To extend the scope of reagent **6**, its reactivity towards miscellaneous electrophiles was also investigated (Table 3).

As already mentioned, in contrast with unactivated ketones, α-keteoesters reacted nicely with **6** and delivered the ester product only.

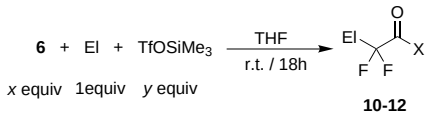


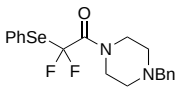
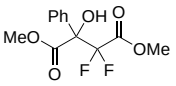
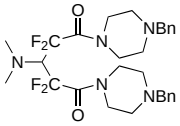
Scheme 7. Krapcho-type reaction after the attack of acyl chlorides by **6**.



Scheme 8. Selective formation of **8**.

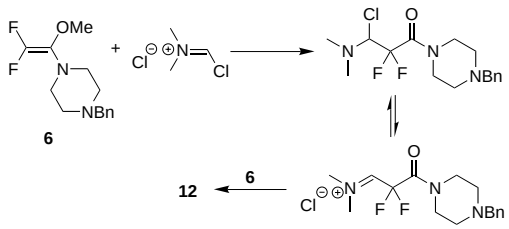
Table 3. Reactions of **6** with miscellaneous electrophiles.



Entry	El	*x*	*y*		Yield (%)[a]
1	PhSeCl	2	2		**10**: 60 (70)
2	methyl phenyloxoacetate	2	2		**11**: 85
3	Vilsmeier's salt[b]	2	2		**12**: 50
4	Vilsmeier's salt[b]	4	4		**12**: 73

[a] Isolated yield. In parentheses crude yield determined by ^{19}F NMR with internal standard ($PhOCF_3$). [b] Commercial form or from DMF/$POCl_3$.

In the case of benzeneselenenyl chloride or chloroiminium chloride, the amidic product was exclusively obtained, again, because of a subsequent Krapcho reaction (entry 1). The Vilsmeier's salt provided a di-substituted compound (entries 3, 4) since the first attack of **6** on this substrate led, after addition–elimination, to another iminium salt which is able to react again with **6** (Scheme 9).



Scheme 9. Reaction of **6** with Vilsmeier's salt.

Conclusion

In summary, this work demonstrates that hemiaminals of fluoral are not only trifluoromethylating agents but also very efficient sources of equivalents of difluoromethylcarboxyl anions which can be transferred on various electrophiles. The exploitation of this strategy for synthetic applications is under study in our laboratory and will be reported in due course.

Experimental Section

General remarks: Solvents were distilled prior use. Other reagents were used as received. ^1H, ^{13}C and ^{19}F NMR spectra were recorded in $CDCl_3$ at 300, 75 and 282 MHz, respectively. Chemical shifts are given in ppm relative to TMS (^1H, ^{13}C) or $CFCl_3$ (^{19}F) as internal references. Coupling constants are given in Hertz. Flash chromatography was performed on Merck silica gel 60M (0.04–0.063 mm). Melting points (uncorrected) were determined in capillary tubes on a Büchi apparatus. Reagent **5** was prepared according to our previous work.[11b]

General procedure for the reaction with aldehydes: A solution of BuLi (2.5 M in hexanes, 0.8 mL, 2 mmol) was added at −78 °C, under nitrogen, to a solution of **5** (0.576 g, 2 mmol) in dry THF (2 mL). The temperature was allowed to rise slowly (for 5 h) to 0 → 10 °C. Then, trimethylsilyl trifluoromethanesulfonate (0.360 mL, 2 mmol) was added, followed, 10 min later, by the aldehyde (1 mmol). After 2 h, the cooling bath was removed and the mixture stirred for 18 h at room temperature. The reaction mixture was then hydrolyzed with aqueous 1 M HCl (2 mL) for 1 h and extracted with dichloromethane. The organic solution was dried over Na_2SO_4 and evaporated under vacuo. The crude product was then purified by flash chromatography (eluents are indicated in parentheses).

General procedure for the reaction with aldehydes followed by LiCl hydrolysis: The same procedure was applied but hydrolysis with HCl was replaced by a treatment with a saturated LiCl aqueous solution.

General procedure for the reaction with acid chlorides or benzeneselenenyl chloride: The same procedure was applied but hydrolysis with HCl was replaced by aqueous hydrolysis.

General procedure for the reaction with Vilsmeier's salt: The same procedure was applied but with 4 equiv **5**, BuLi and $TfOSiMe_3$ and hydrolysis with HCl was replaced by aqueous hydrolysis.

Methyl 2,2-difluoro-3-hydroxy-3-phenylpropanoate (7a): (petroleum ether/ether 19:1 then 4:1, yellow oil). ^1H NMR: $\delta = 7.44–7.34$ (m, 5H), 5.16 (dd, $J = 16.1$, $J = 7.1$ Hz, 1H), 3.84 (s, 3H); ^{13}C NMR: $\delta = 164.6$ (dd, $J = 32.8$, $J = 31.0$ Hz), 134.92 (d, $J = 1.7$ Hz), 129.7, 128.8, 128.1, 114.4 (dd, $J = 259.5$, $J = 253.7$ Hz), 74.0 (dd, $J = 28.2$, $J = 24.1$ Hz), 53.9; ^{19}F NMR: $\delta = -113.6$ (dd, $J = 262.7$, $J = 7.1$ Hz, 1F), −121.4 (dd, $J = 262.7$, $J = 16.1$ Hz, 1F); elemental analysis calcd (%) for $C_{10}H_{10}F_2O_3$: C 55.56, H 4.66; found: C 55.34, H 4.84.

1-(4-Benzylpiperazino)-2,2-difluoro-3-hydroxy-3-phenyl-1-propanone (8a): (petroleum ether/ether 4:1, yellow oil). ^1H NMR: $\delta = 7.37–7.28$ (m, 10H), 5.28 (dd, $J = 21.9$, $J = 3.0$ Hz, 1H), 3.70 (m, 4H), 3.54 (s, 2H), 2.54–2.44 (m, 4H); ^{13}C NMR: $\delta = 162.85$ (t, $J = 28.9$ Hz), 137.8, 135.0 (d, $J = 1.6$ Hz), 129.5, 129.1, 128.8, 128.8 (t, $J = 1.1$ Hz), 128.4, 127.8, 115.4 (dd, $J = 259.1$, $J = 267.3$ Hz), 74.0 (dd, $J = 29.1$, $J = 23.1$ Hz), 53.3, 52.9, 46.2 (dd, $J = 6.9$, $J = 5.8$ Hz), 43.5; ^{19}F NMR: $\delta = -103.7$ (dd, $J = 291.1$, $J = 3.0$ Hz, 1F),

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– 118.2 (dd, $J = 291.1$, $J = 21.9$ Hz, 1F); elemental analysis calcd (%) for $C_{20}H_{22}F_2N_2O_2$: C 66.65, H 6.15, N 7.77; found: C 66.92, H 6.18, N 8.06.

Methyl 2,2-difluoro-3-hydroxy-3-(2-naphthyl)propanoate (7b): (petroleum ether/ether 9:1 then 4:1, white solid). M.p. 90 °C; ^{1}H NMR: $\delta = 7.88 – 7.85$ (m, 4H), 7.58 – 7.51 (m, 3H), 5.35 (dd, $J = 15.8$, $J = 7.5$ Hz, 1H), 3.87 (s, 3H); ^{13}C NMR: $\delta = 164.5$ (dd, $J = 32.7$, $J = 31.0$ Hz), 134.1, 133.3, 132.3 (t, $J =$ 1.1 Hz), 128.7, 128.6, 128.1, 127.9 (t, $J = 1.1$ Hz), 127.1, 126.8, 125.1 (t, $J =$ 1.4 Hz), 114.4 (dd, $J = 259.9$, $J = 253.9$ Hz), 74.3 (dd, $J = 28.0$, $J = 24.1$ Hz), 53.9; ^{19}F NMR: $\delta = -113.3$ (dd, $J = 263.5$, $J = 7.9$ Hz, 1F), – 120.8 (dd, $J =$ 263.5, $J = 15.6$ Hz, 1F); elemental analysis calcd (%) for $C_{14}H_{12}F_2O_3$: C 63.16, H 4.54; found: C 63.03, H 4.89.

Methyl 2,2-difluoro-3-hydroxyheptanoate (7c): (petroleum ether/acetone 19:1, yellow viscous oil). ^{1}H NMR: $\delta = 4.03$ (dddd, $J = 9.8$, $J = 14.9$, $J = 7.4$, $J = 2.8$ Hz, 1H), 3.92 (s, 3H), 1.72 – 1.22 (m, 6H), 2.4 (br s, 1H), 0.94 (t, $J =$ 7.2 Hz, 3H); ^{13}C NMR: $\delta = 164.6$ (dd, $J = 32.9$, $J = 31.3$ Hz), 115.2 (dd, $J =$ 256.9, $J = 254.1$ Hz), 72.1 (dd, $J = 27.2$, $J = 25.0$ Hz), 53.8, 29.2 (dd, $J = 3.0$, $J = 1.9$ Hz), 27.7, 22.7, 14.2; ^{19}F NMR: $\delta = -114.9$ (dd, $J = 264.1$, $J = 7.4$ Hz, 1F), – 122.9 (dd, $J = 264.1$, $J = 14.9$, 1F); elemental analysis calcd (%) for $C_8H_{14}F_2O_3$: C 48.98, H 7.19; found: C 49.15, H 7.28.

1-(4-Benzylpiperazino)-2,2-difluoro-3-hydroxy-1-heptanone (8c): (Petroleum ether/acetone 19:1, yellow viscous oil). ^{1}H NMR: $\delta = 7.34 – 7.28$ (m, 5H), 4.08 (m, 1H), 3.76 (m, 2H), 3.67 (m, 2H), 3.55 (s, 2H), 2.51 (m, 4H), 1.68 – 1.27 (m, 6H), 0.94 (t, $J = 7.127$, 3H); ^{13}C NMR: $\delta = 162.7$ (t, $J =$ 29.427), 137.8, 129.5, 128.8, 127.8, 116.5 (dd, $J = 265.4$, $J = 259.327$), 72.2 (dd, $J = 28.3$, $J = 24.427$), 63.1, 53.4, 52.9, 46.2 (dd, $J = 7.1$, $J = 5.527$), 43.3, 28.2 (dd, $J = 3.3$, $J = 2.227$), 28.1, 22.9, 14.4; ^{19}F NMR: $\delta = -107.1$ (d, $J =$ 291.127, 1F), – 118.7 (dd, $J = 291.1$, $J = 19.5$ Hz, 1F); elemental analysis calcd (%) for $C_{18}H_{26}F_2N_2O_2$: C 63.51, H 7.70, N 8.23; found: C 63.39, H 7.61, N 7.94.

Methyl 2,2-difluoro-3-hydroxy-3-(6-methoxy-2-naphthyl) propanoate (7d): (Petroleum ether/acetone 9:1, beige solid). M.p. 105 °C; ^{1}H NMR: $\delta = 7.83$ (s, 1H), 7.78 – 7.71 (m, 2H), 7.52 (m, 1H), 7.21 – 7.14 (m, 2H), 5.31 (dd, $J =$ 15.9, $J = 7.9$ Hz, 1H), 3.94 (s, 3H), 3.86 (s, 3H); ^{13}C NMR: $\delta = 164.6$ (dd, $J = 31.0$, $J = 36.7$ Hz), 158.6, 135.3, 130.14, 130.11, 128.8, 127.7, 127.5, 125.8 (t, $J = 1.4$ Hz), 119.7, 114.5 (dd, $J = 253.0$, $J = 259.6$ Hz), 106.0, 74.2 (dd, $J =$ 28.0, $J = 24.1$ Hz), 55.7, 53.9; ^{19}F NMR: $\delta = -113.6$ (dd, $J = 262.9$, $J =$ 7.9 Hz, 1F), – 120.8 (dd, $J = 262.9$, $J = 15.9$ Hz, 1F); elemental analysis calcd (%) for $C_{15}H_{14}F_2O_4$: C 60.81, H 4.76; found: C 60.98, H 4.83.

1-(4-Benzylpiperazino)-2,2-difluoro-3-hydroxy-3-(6-methoxy-2-naphthyl)-1-propanone (8d): (Petroleum ether/acetone 9:1, beige solid). M.p. 130 °C; ^{1}H NMR: $\delta = 7.91$ (s, 1H), 7.80 – 7.76 (m, 2H), 7.59 (m, 1H), 7.38 – 7.27 (m, 5H), 7.22 – 7.17 (m, 2H), 5.42 (dd, $J = 20.9$, $J = 3.2$ Hz, 1H), 4.35 (br s, 1H), 3.94 (s, 3H), 3.71 (m, 4H), 3.52 (s, 2H), 2.52 (m, 2H), 2.43 (m, 2H); ^{13}C NMR: $\delta = 162.9$ (dd, $J = 29.4$, $J = 28.3$ Hz), 158.4, 137.7, 135.6, 134.15, 134.11, 129.5, 128.85, 128.80, 128.1, 127.8, 126.9, 126.7 (t, $J = 1.6$ Hz), 119.4, 115.6 (dd, $J = 258.5$, $J = 267.3$ Hz), 106.0, 74.2 (dd, $J = 29.1$, $J = 23.0$ Hz), 63.1, 55.7, 53.3, 52.9, 46.2 (t, $J = 6.3$ Hz), 43.5; ^{19}F NMR: $\delta = -103.4$ (dd, $J =$ 291.4, $J = 3.2$ Hz, 1F), – 117.8 (dd, $J = 291.4$, $J = 20.9$ Hz, 1F); elemental analysis calcd (%) for $C_{25}H_{26}F_2N_2O_3$: C 68.17, H 5.95, N 6.36; found: C 67.95, H 6.02, N 6.07.

Methyl 2,2-difluoro-3-hydroxydecanoate (7e): (petroleum ether/acetone 19:1, yellow oil). ^{1}H NMR: $\delta = 4.03$ (dddd, $J = 2.7$, $J = 9.8$, $J = 15.0$, $J =$ 7.5 Hz, 1H), 3.92 (s, 3H), 2.3 (br s, 1H), 1.71 – 1.20 (m, 12H), 0.90 (t, $J =$ 6.7 Hz, 3H); ^{13}C NMR: $\delta = 164.6$ (dd, $J = 31.3$, $J = 32.9$ Hz), 115.2 (dd, $J =$ 256.9, $J = 254.1$ Hz), 72.1 (dd, $J = 25.3$, $J = 27.4$ Hz), 53.8, 32.1, 29.6, 29.52 (dd, $J = 1.4$, $J = 1.9$ Hz), 29.47, 25.6, 23.0, 14.5; ^{19}F NMR: $\delta =$ -115.0 (dd, $J =$ 264.1, $J = 7.5$ Hz, 1F), – 123.0 (dd, $J = 264.1$, $J = 15.0$ Hz, 1F); elemental analysis calcd (%) for $C_{11}H_{20}F_2O_3$: C 55.45, H 8.46; found: C 55.53, H 8.73.

1-(4-Benzylpiperazino)-2,2-difluoro-3-hydroxy-1-decanone (8e): (petroleum ether/acetone 19:1, yellow viscous oil). ^{1}H NMR: $\delta = 7.36 – 7.27$ (m, 5H), 4.18 (m, 1H), 3.76 (m, 2H), 3.68 (m, 2H), 3.55 (s, 2H), 2.52 (m, 4H), 1.68 – 1.21 (m, 12H), 0.9 (t, $J = 6.4$ Hz, 3H); ^{13}C NMR: $\delta = 162.75$ (dd, $J =$ 29.1 Hz), 137.7, 129.5, 128.8, 127.8, 116.5 (dd, $J = 259.1$, $J = 265.1$ Hz),72.24 (dd, $J = 24.1$, $J = 28.5$ Hz), 63.1, 53.4, 52.8, 46.2 (dd, $J = 7.1$, $J = 5.5$ Hz), 43.2, 32.2, 29.8, 29.6, 28.5 (dd, $J = 3.6$, $J = 1.9$ Hz), 25.9, 23.0, 14.5; ^{19}F NMR: $\delta =$ – 103.4 (d, $J = 291.4$ Hz, 1F), – 117.8 (dd, $J = 291.4$, $J = 20.6$ Hz, 1F); elemental analysis calcd (%) for $C_{21}H_{32}F_2N_2O_2$: C 65.94, H 8.43, N 7.32; found: C 66.09, H 8.67, N 7.68.

Methyl 2,2-difluoro-3-hydroxy-3-(3-thienyl)propanoate (7f): (petroleum ether/acetone 9:1, yellow viscous oil). ^{1}H NMR: $\delta = 7.42 – 7.32$ (m, 2H), 7.18 (m, 1H), 5.27 (m, 1H), 3.87 (s, 3H), 3.2 (br s, 1H); ^{13}C NMR: $\delta = 164.4$ (dd, $J = 31.3$, $J = 32.9$ Hz), 136.1 (d, $J = 2.2$ Hz), 126.9 (t, $J = 1.7$ Hz), 126.7, 125.1 (t, $J = 1.4$ Hz), 114.2 (dd, $J = 259.1$, $J = 254.1$ Hz), 70.7 (dd, $J = 25.3$, $J =$ 28.5 Hz), 53.9; ^{19}F NMR: $\delta = -113.8$ (dd, $J = 262.7$, $J = 8.0$ Hz, 1F), – 120.9 (dd, $J = 262.7$, $J = 16.1$ Hz, 1F); elemental analysis calcd (%) for $C_8H_8F_2O_3S$: C 43.24, H 3.63, S 14.43; found: C 42.96, H 3.65, S 14.05.

1-(4-Benzylpiperazino)-2,2-difluoro-3-hydroxy-3-(3-thienyl)-1-propanone (8f): (petroleum ether/acetone 9:1, white solid). M.p. 101 °C; ^{1}H NMR: $\delta =$ 7.44 (m, 1H), 7.36 – 7.28 (m, 6H), 7.21 (m, 1H), 5.36 (dd, $J = 20.4$, $J = 3.2$ Hz, 1H), 3.72 (m, 4H), 3.57 (s, 2H), 2.52 (m, 4H); ^{13}C NMR: $\delta = 162.7$ (t, $J =$ 28.8 Hz), 137.4, 136.1 (d, $J = 1.7$ Hz), 129.6, 128.8, 127.9, 127.5 (t, $J = 1.7$ Hz), 125.8, 124.9 (t, $J = 1.4$ Hz), 115.2 (dd, $J = 267.0$, $J = 258.8$ Hz), 71.1 (dd, $J =$ 23.6, $J = 30.2$ Hz), 63.0, 53.3, 52.8, 46.1 (dd, $J = 6.9$, $J = 5.8$ Hz), 43.3; ^{19}F NMR: $\delta = -104.0$ (dd, $J = 290.8$, $J = 3.2$ Hz, 1F), – 117.0 (dd, $J = 290.8$, $J =$ 20.4 Hz, 1F); elemental analysis calcd (%) for $C_{18}H_{20}F_2N_2O_2S$: C 59.00, H 5.50, N 7.65; found: C 59.31, H 5.47, N 7.92.

Methyl (*E*)-2,2-difluoro-3-hydroxy-5-phenyl-4-pentenoate (7g): (petroleum ether/acetone 19:1, yellow viscous oil). ^{1}H NMR: $\delta = 7.45 – 7.27$ (m, 5H), 6.82 (d, $J = 16.0$ Hz, 1H), 6.26 (dd, $J = 6.5$, $J = 16.0$ Hz, 1H), 4.77 (dddd, $J = 6.5$, $J = 14.3$, $J = 7.9$, $J = 1.2$ Hz, 1H), 3.92 (s, 3H), 2.9 (br s, 1H); ^{13}C NMR: $\delta = 164.3$ (dd, $J = 31.3$, $J = 32.4$ Hz), 136.4, 136.1, 129.1, 129.0, 127.3, 121.9 (dd, $J = 3.3$, $J = 2.2$ Hz), 114.5 (dd, $J = 258.0$, $J = 254.1$ Hz), 73.3 (dd, $J = 25.0$, $J = 28.3$ Hz), 53.9; ^{19}F NMR: $\delta = -113.9$ (dd, $J = 263.5$, $J =$ 7.9 Hz, 1F), – 121.3 (dd, $J = 263.5$, $J = 14.3$ Hz, 1F); elemental analysis calcd (%) for $C_{12}H_{12}F_2O_3$: C 59.50, H 4.99; found: C 59.63, H 5.13.

(*E*)1-(4-Benzyl-piperazin-1-yl)-2,2-difluoro-3-hydroxy-5-phenylpent-4-en-1-one (8g): (petroleum ether/acetone 19:1, white solid). M.p. 96 °C; ^{1}H NMR: $\delta = 7.45 – 7.28$ (m, 10H), 6.86 (d, $J = 16.0$ Hz, 1H), 6.34 (dd, $J = 6.2$, $J = 16.0$ Hz, 1H), 4.82 (dddd, $J = 6.2$, $J = 17.2$, $J = 1.2$, $J = 5.5$ Hz, 1H), 3.77 (m, 2H), 3.70 (m, 2H), 3.56 (s, 2H), 2.53 (m, 4H); ^{13}C NMR: $\delta =$ 162.4 (t, $J = 28.8$ Hz), 137.7, 136.6, 135.4, 129.6, 129.0, 128.8, 128.5, 127.8, 127.2, 122.7 (t, $J = 3.0$ Hz), 115.8 (dd, $J = 265.4$, $J = 259.9$ Hz), 73.6 (dd, $J =$ 28.5, $J = 24.7$ Hz), 53.4, 52.9, 46.2 (dd, $J = 7.1$, $J = 5.5$ Hz), 43.3; ^{19}F NMR: $\delta = -105.1$ (dd, $J = 290.5$, $J = 5.5$ Hz, 1F), – 114.8 (dd, $J = 290.5$, $J =$ 17.2 Hz, 1F); elemental analysis calcd (%) for $C_{22}H_{24}F_2N_2O_2$: C 68.38, H 6.26, N 7.25; found: C 68.52, H 6.02, N 7.32.

Methyl 2,2-difluoro-3-hydroxy-3-(*N*-Boc-1*H*-indol-3-yl) propanoate (7h): (petroleum ether/acetone 19:1, yellow viscous oil). ^{1}H NMR: $\delta = 8.15$ (d, $J = 8.1$ Hz, 1H), 7.75 (s, 1H), 7.69 (d, $J = 7.7$ Hz, 1H), 7.37 – 7.22 (m, 2H), 5.47 (dd, $J = 16.3$, $J = 7.7$ Hz, 1H), 3.85 (s, 3H), 1.67 (s, 9H); ^{13}C NMR: $\delta =$ 164.5 (dd, $J = 31.0$, $J = 32.7$ Hz), 149.9, 135.8, 129.1, 125.9, 125.2, 123.3, 120.4, 115.6, 115.3 (d, $J = 2.8$ Hz), 114.7 (dd, $J = 253.6$, $J = 259.1$ Hz), 84.8, 68.3 (dd, $J = 25.0$, $J = 29.4$ Hz), 53.9, 28.5; ^{19}F NMR: $\delta = -113,2$ (dd, $J =$ 259.5, $J = 7.7$ Hz, 1F), – 120.3 (dd, $J = 259.5$, $J = 16.3$ Hz, 1F); elemental analysis calcd (%) for $C_{17}H_{19}F_2NO_5$: C 57.46, H 5.69; found: C 57.25, H 5.37.

1-(4-Benzylpiperazino)-2,2-difluoro-3-hydroxy-3-(*N*-Boc-1*H*-indol-3-yl)-1-propanone (8h): (petroleum ether/acetone 19:1, yellow solid). M.p. 150 °C; ^{1}H NMR: $\delta = 8.19$ (d, $J = 8.1$ Hz, 1H), 7.76 (s, 1H), 7.70 (d, $J =$ 7.7 Hz, 1H), 7.35 – 7.25 (m, 7H), 5.59 (dd, $J = 21.4$, $J = 2.7$ Hz, 1H), 3.73 (m, 4H), 3.55 (s, 2H), 2.56 – 2.45 (m, 4H), 1.69 (s, 9H); ^{13}C NMR: $\delta = 162.7$ (t, $J = 28.8$ Hz), 149.9, 137.7, 135.8, 129.7, 129.5, 128.8, 127.8, 126.1, 124.9, 123.2, 120.6, 115.8 (dd, $J = 267.6$, $J = 259.3$ Hz), 115.6, 115.1 (d, $J = 1.6$ Hz), 84.3, 68.9 (dd, $J = 23.4$, $J = 31.0$ Hz), 63.1, 53.3, 52.9, 46.3 (dd, $J = 6.6$, $J = 5.5$ Hz), 43.5, 28.6; ^{19}F NMR: $\delta = -103.9$ (dd, $J = 291.1$, $J = 2.7$ Hz, 1F), – 117.0 (dd, $J = 291.1$, $J = 21.4$ Hz, 1F); elemental analysis calcd (%) for $C_{27}H_{31}F_2N_3O_4$: C 64.92, H 6.25, N 8.41; found: C 64.64, H 6.19, N 8.27.

1-(4-Benzylpiperazino)-2,2-difluoro-3-phenyl-1,3-propanedione (9a): (petroleum ether/ether 4:1, yellow oil). ^{1}H NMR: $\delta = 8.13 – 8.08$ (m, 2H), 7.67 (m, 1H), 7.55 – 7.48 (m, 2H), 7.36 – 7.28 (m, 5H), 3.69 (m, 4H), 3.55 (s, 2H), 2.50 (m, 4H); ^{13}C NMR: $\delta = 187.1$ (t, $J = 26.9$ Hz), 160.5 (t, $J = 27.2$ Hz), 137.4, 135.2, 132.0 (t, $J = 1.1$ Hz), 130.6 (t, $J = 2.7$ Hz), 129.6, 129.2, 128.8, 127.9, 112.1 (t, $J = 264.5$ Hz), 63.0, 53.2, 52.7, 46.0 (t, $J = 4.7$ Hz), 43.6; ^{19}F NMR: $\delta = -102.9$ (s); elemental analysis calcd (%) for $C_{20}H_{20}F_2N_2O_2$: C 67.03, H 5.62, N 7.82; found: C 67.15, H 5.97, N 7.59.

1-(4-Benzylpiperazino)-3-cyclopropyl-2,2-difluoro-1,3-propanedione (9b): (petroleum ether/acetone 9:1, yellow viscous oil). ^{1}H NMR: $\delta = 7.34 – 7.28$ (m, 5H), 3.66 (m, 4H), 3.54 (s, 2H), 2.49 (m, 4H), 2.31 (m, 1H), 1.31 – 1.15 (m, 4H); ^{13}C NMR: $\delta = 198.2$ (t, $J = 27.4$ Hz), 160.1 (t, $J = 26.9$), 137.8, 129.5, 128.8, 127.8, 111.3 (t, $J = 265.7$ Hz), 63.1, 53.3, 52.8, 45.9 (t, $J =$ 4.7 Hz), 43.5, 17.3, 14.0; ^{19}F NMR: $\delta = -109.2$ (s); elemental analysis calcd

(%) for $C_{17}H_{20}F_2N_2O_2$: C 63.34, H 6.25, N 8.69; found: C 63.53, H 6.18, N 9.02.

1-(4-Benzylpiperazino)-2,2-difluoro-2-(benzeneselenenyl)-1-ethanone (10): (petroleum ether/acetone 19:1, yellow solid). M.p. 57 °C; ^{1}H NMR: $\delta = 7.78 - 7.73$ (m, 2H), 7.48 – 7.28 (m, 8H), 3.69 (m, 4H), 3.55 (s, 2H), 2.49 (m, 4H); ^{13}C NMR: $\delta = 160.6$ (t, $J = 25.0$ Hz), 138.0, 137.9, 130.2, 129.6, 129.5, 128.9, 127.8, 124.5, 123.9 (t, $J = 306.5$ Hz), 63.1, 53.4, 52.9, 46.2 (t, $J = 5.2$ Hz), 44.1; ^{19}F NMR: $\delta = -71.2$ (s); elemental analysis calcd (%) for $C_{19}H_{20}F_2N_2OSe$: C 55.75, H 4.92, N 6.84, Se 19.29; found: C 56.04, H 4.87, N 6.99, Se 18.95.

Dimethyl 2,2-difluoro-3-hydroxy-3-phenylsuccinate (11): (petroleum ether/acetone 9:1, yellow oil). ^{1}H NMR: $\delta = 7.84 - 7.80$ (m, 2H), 7.44 – 7.40 (m, 3H), 4.5 (br s, 1H), 3.96 (s, 3H), 3.85 (s, 3H); ^{13}C NMR: $\delta = 170.9$, 163.5 (dd, $J = 31.3$, 32.4 Hz), 133.6, 129.7, 128.6, 127.4 (t, $J = 1.9$ Hz), 113.5 (dd, $J = 262.9$, $J = 265.7$ Hz), 77.5 (t, $J = 31.8$ Hz), 54.8, 54.0; ^{19}F NMR: $\delta = -108.7$ (d, $J = 268.5$ Hz, 1F), -115.1 (d, $J = 268.5$ Hz, 1F); elemental analysis calcd (%) for $C_{12}H_{12}F_2O_5$: C 52.56, H 4.41; found: C 52.81, H 4.49.

1,5-Bis(4-benzylpiperazino)-3-(dimethylamino)-2,2,4,4-tetrafluoro-1,5-pentanedione (12): (petroleum ether/acetone 9:1, yellow viscous oil). ^{1}H NMR: $\delta = 7.31 - 7.27$ (m, 10H), 4.9 (tt, $J = 15.8$, $J = 13.7$ Hz, 1H), 3.82 – 3.62 (m, 8H), 3.54 (s, 4H), 2.66 (s, 6H), 2.50 (m, 8H); ^{13}C NMR: $\delta = 161.6$ (t, $J = 27.6$ Hz), 137.9, 129.5, 128.8, 127.8, 119.4 (t, $J = 265.5$ Hz), 63.9 (quint, $J = 21.1$ Hz), 63.1, 53.5, 53.0, 46.3 (br s), 44.0, 43.7; ^{19}F NMR: $\delta = -101.1$ (dd, $J = 293.7$, $J = 15.8$ Hz, 2F), -106.2 (dd, $J = 293.7$, $J = 13.7$ Hz, 2F).

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[1] B. E. Smart, *J. Fluorine Chem.* **2001**, *109*, 3 – 11.
[2] a) J. T. Welch, S. Eswarakrishnan, *Fluorine in Bioorganic Chemistry*, Wiley, New York, **1991**; b) *Biomedical Frontiers of Fluorine Chemistry* (Eds.: I. Ojima, J. R. McCarthy, J. T. Welch), ACS Symposium Series 639, American Chemical Society, Washington DC, **1996**; c) *Fluorine-containing Amino Acids. Synthesis and Properties* (Eds.: V. P. Kukhar, V. A. Soloshonok), Wiley, Chichester, **1995**; d) T. Hiyama, *Organofluorine Compounds*: *Chemistry and Properties*, Springer, Berlin, **2000**, Chapter 5, pp. 137 – 182.
[3] For a review see: a) M. J. Tozer, T. F. Herpin, *Tetrahedron* **1996**, *52*, 8619 – 8683; b) J. M. Percy, *Contemp. Org. Synth.* **1995**, 251 – 268; c) K. Uneyama, *J. Synth. Org. Jpn.* **1993**, *51*, 232 – 246.
[4] a) J. Fried, E. A. Hallinan, *Tetrahedron Lett.* **1984**, *25*, 2301 – 2302; b) M. Kuroboshi, T. Ishihara, *Bull. Chem. Soc. Jpn* **1990**, *63*, 428 – 437; c) R. W. Lang, B. Schaub, *Tetrahedron Lett.* **1988**, *29*, 2943 – 2946; d) T. Tsukamoto, T. Kitazume, *J. Chem. Soc. Perkin Trans. 1* **1993**, 1177 – 1181.
[5] a) C. Portella, T. Brigaud, O. Lefebvre, R. Plantier-Royon, *J. Fluorine Chem.* **2000**, *101*, 193 – 198; b) R. Plantier-Royon, C. Portella, *Carbohydr. Res.* **2000**, *327*, 119 – 146.
[6] K. Uneyama, K. Maeda, T. Kato, T. Katagiri, *Tetrahedron Lett.* **1998**, *39*, 3741 – 3744.
[7] a) K. Uneyama, G. Mitzutani, *Chem. Commun.* **1999**, 613 – 614; b) K. Uneyama, G. Mitzutani, K. Maeda, T. Kato, *J. Org. Chem.* **1999**, *64*, 6717 – 6723.
[8] a) H. Amii, T. Kobayashi, Y. Hatamoto, K. Uneyama, *Chem. Commun.* **1999**, 1323 – 1324; b) H. Amii, T. Kobayashi, K. Uneyama, *Synthesis* **2000**, 2001 – 2003.
[9] a) Y. Xu, W. R. Dolbier Jr, X. X. Rong, *J. Org. Chem.* **1997**, *62*, 1576 – 1577; b) Y. Ding, J. Wang, K. A. Abboud, Y. Xu, W. R. Dolbier Jr, N. G. J. Richards, *J. Org. Chem.* **2001**, *66*, 6381 – 6388.
[10] a) T. Billard, B. R. Langlois, G. Blond, *Tetrahedron Lett.* **2000**, *41*, 8777 – 8780; b) T. Billard, B. R. Langlois, G. Blond, *Eur. J. Org. Chem.* **2001**, 1467 – 1471; c) G. Blond, T. Billard, B. R. Langlois, *Tetrahedron Lett.* **2001**, *42*, 2473 – 2475.
[11] a) G. Blond, T. Billard, B. R. Langlois, *J. Org. Chem.* **2001**, *66*, 4826 – 4830; b) T. Billard, B. R. Langlois, *J. Org. Chem.* **2002**, *67*, 997 – 1000.
[12] C. Hansch, A. Leo, R. W. Taft, *Chem. Rev.* **1991**, *91*, 165 – 195.
[13] a) J. Augé, F. Leroy, *Tetrahedron Lett.* **1996**, *37*, 7715 – 7716; b) H. Firouzabadi, B. Karimi, S. Eslami, *Tetrahedron Lett.* **1999**, *40*, 4055 – 4058; c) V. G. Saraswathy, S. Sankararaman, *J. Org. Chem.* **1994**, *59*, 4665 – 4670.
[14] A. F. Carey, R. J. Sundberg, *Advanced Organic Chemistry*, *Vol. A*, Plenum Press, New York, **1990**, p. 422.
[15] a) L. A. Carpino, M. Beyermann, H. Wenschuh, M. Bienert, *Acc. Chem. Res.* **1996**, *29*, 268 – 274; b) L. A. Carpino, D. Ionescu, A. El-Faham, *Tetrahedron Lett.* **1998**, *39*, 241 – 244.

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