Mixed Organofluorine−Organosilicon Chemistry. 13. One-Pot Synthesis of Difluoroaldols from Acylsilanes and Trifluoromethyltrimethylsilane. Application to the Synthesis of a Difluoro Analogue of Egomaketone

Olivier Lefebvre, Thierry Brigaud,* and Charles Portella*

Laboratoire "Réactions Sélectives et Applications", Associé au CNRS (UMR 6519), Université de Reims Champagne-Ardenne, Faculté des Sciences, BP 1039, 51687 Reims Cedex 2, France

thierry.brigaud@univ-reims.fr

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Difluoroaldol compounds **3** were synthesized in a one-pot procedure involving an acylsilane **1**, trifluoromethyltrimethylsilane (TFMTMS), and an aldehyde. The key intermediate of this reaction is a difluoroenoxysilane **2.** Ytterbium triflate proved to be a very efficient catalyst for promoting the aldol type reaction under very mild conditions. The potential of this reaction for the convergent synthesis of difluorinated compounds was illustrated by the synthesis of difluoroegomaketone **7d** through dehydration of the corresponding aldol compound **3d**.

Introduction

The introduction of a difluoromethylene unit into an organic molecule presents a significant importance in bioorganic and medicinal chemistry.[1] More precisely, due to their strong electron-withdrawing effect, fluorine atoms activate the hydration of an adjacent carbonyl group when they are introduced in the α position. This hydrate acts as a transition state mimic for ester and amide bond cleavage. Therefore, numerous bioactive compounds containing the difluoromethylene ketone unit are inhibitors of HIV-1 protease,[2] elastase,[3] renin,[4] and human heart chymase.[5]

The aldol reaction is a powerful synthetic tool for the creation of carbon−carbon bonds, and its application to the synthesis of functionalized α,α-difluorocarbonyl compounds has proven to be very productive. Besides difluoroenolate chemistry,[6] successful aldol-type reactions have been reported from difluoroenol ethers,[7] difluoroketene silyl acetals,[8] and difluoroenoxysilanes. The latter were prepared from chlorodifluoromethyl ketones,[9] trifluoroacetylsilane,[10] and trifluoromethyl ketones.[11] These procedures produce metal wastes or use solvents incompatible with Lewis acids, so the difluoroenoxysilane has to be isolated before performing the aldol reaction. Moreover, these procedures need the preliminary synthesis of a fluorinated substrate. We report here a highly convergent one-pot procedure for the synthesis of α,α-difluoro-*β*-hydroxy ketones starting from an acylsilane, trifluoromethyltrimethylsilane (TFMTMS), and an aldehyde. The key intermediate of this reaction is a difluoroenoxysilane whose reactivity in Michael additions,[12] glycosylations,[13] allylations and benzylations,[14,15] and aldol reactions with benzaldehyde[14] and acylsilanes[16] has

* To whom correspondence should be addressed. thierry.brigaud@univ-reims.fr or charles.portella@univ-reims.fr.

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Scheme 1

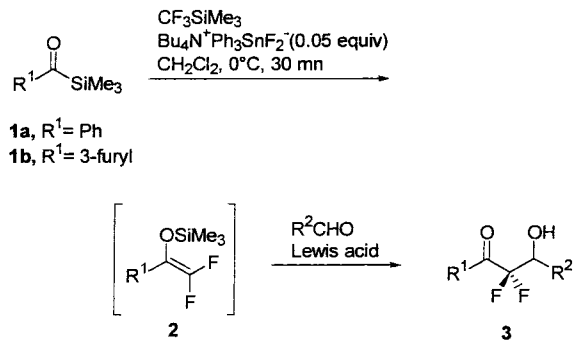
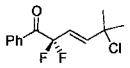


Table 1. One-Pot Aldol Reaction with Various Lewis Acids

Entry	R^1	R^2	Lewis acid	Aldol (% yield)[a,b]
1	Ph	Ph	$TiCl_4$ (1.5 equiv)	**3a** (71)
2	Ph	Ph	$BF_3.OEt_2$ (1.2 equiv)	**3a** (78)
3	Ph		$TiCl_4$ (1.5 equiv)	**3b** (58)
4	Ph		$BF_3.OEt_2$ (1.2 equiv)	**3c** (61)
5	3-furyl		$BF_3.OEt_2$ (1.2 equiv)	**3d** (69)
6	Ph		$TiCl_4$ (1.2 equiv)	**3e** (14) +  **3f** (41)
7	Ph		$BF_3.OEt_2$ (1.2 equiv)	**3e** (69)
8	Ph		$Yb(OTf)_3$ (0.01 equiv)	**3e** (78)

[a] Isolated yield. [b] Overall yield based on the starting acylsilane.

already been reported by our group. This strategy, applied to the aldol reaction, has allowed a short synthesis of a fluorinated analogue of the furan monoterpenoid egomaketone.

Results and Discussion

Lewis Acid-Catalyzed One-pot Aldol Reactions. The chain reaction of TFMTMS with an acylsilane under fluoride activation giving a difluoroenoxysilane can be achieved with the same efficiency in ether, THF, or dichloromethane[14] which is the standard solvent for Mukaiyama type aldol reactions.[17] Therefore, the difluoroenoxysilanes **2** were quantitatively generated in dichloromethane from the reaction of acylsilane **1** and TFMTMS under tetrabutylammonium difluorotriphenylstannate (DFTPS) initiation. The aldehyde and a Lewis acid were then added to the solution. The reaction was first carried out with a stoichiometric amount of conventional Lewis acids ($TiCl_4$ or $BF_3{\cdot}OEt_2$) added at low-temperature, giving the expected aldol compounds in a good yield despite the one-pot process (Scheme 1, Table 1). The reaction was applied to aromatic, aliphatic, and ethylenic aldehydes. It is worth noting that $TiCl_4$ was not suitable to use in aldol reactions with unsaturated aldehydes (Table 1, entry 6). In this case, the major product was the chlorinated compound **3f** probably resulting from a S_N' reaction of the intermediate titanium oxide. We can assume that the chlorination took place in situ and did not occur during hydrolysis because aldol **3e** did not give **3f** when treated under hydrolysis conditions. Furthermore, it is known that S_N' chlorination of this kind of allylic alcohol in the non-fluorinated series required stronger acidic conditions (12 N hydrochloric acid)[18] than that used in our workup procedure. This side reaction could easily be avoided by using $BF_3{\cdot}OEt_2$ as the Lewis acid to give the unique compound **3e** (Table 1, entry 7). The use of lanthanide salts such as $Yb(OTf)_3$ as catalyst is one of the major improvements of the last few years in aldol type reactions.[19] Our one-pot reaction proceeded smoothly at room temperature with only 10% $Yb(OTf)_3$ to give **3e** in 78% yield (Table 1, entry 8). With this mild catalyst, both free hydroxy- and trimethylsilyl-protected aldol **3g** and **3h** were obtained (Table 2, entry 1). In a standard procedure, removal of the trimethylsilyl protecting group was achieved by workup with fluoride ions. Difluoroaldol compounds were then obtained in good yield in a very convergent way starting from aromatic or aliphatic acylsilanes and aldehydes (Scheme 2, Table 2). The reaction with α,*β*-unsaturated aldehydes selectively gave the aldol compounds **3e**−**j** (Table 2, entries 4, 5, 6, 8). No Michael adducts were obtained as we observed with enones.[12] It should be noticed that the aliphatic aldol **3k** (Table 2, entry 6) was the only one to be isolated as the hydrate.

Construction of the α,α-Difluoro-*β*,*γ*-unsaturated Ketone Unit. Synthesis of Difluoroegomaketone. In the course of our studies on *gem*-difluoroterpene analogues synthesis, we recently demonstrated the usefulness of difluoroenoxysilanes to build, in a one-pot reaction, the difluorohomoallylic and difluorohomobenzylic units of difluorodehydro-*ar*-curcumene and difluoro-*ar*-turmerone, respectively.[15] We now present an application of the one-pot aldol reaction to the synthesis of a difluoro analogue of egomaketone.[20] Such a compound, possessing a difluoroallylic moiety, could be reached by a formal *β*,*γ*-dehydration of the corresponding difluoroaldol **3d** (Scheme 3). This transformation proved to be problematic, and appropriate conditions had to be found. The aldol **3c** was used as a model to determine suitable conditions for this reaction. Due to the electron-withdrawing effect of fluorine, the acid-catalyzed dehydration of difluoroaldol **3c**

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Scheme 2

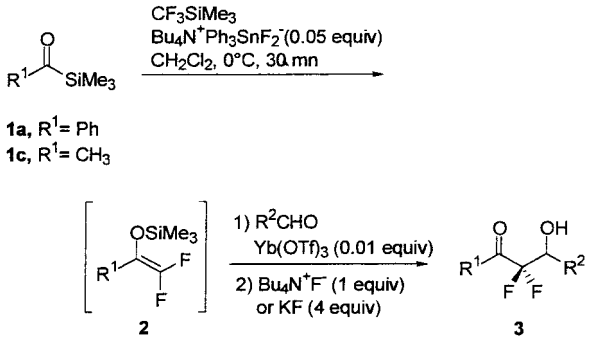
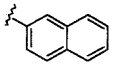
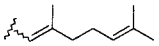
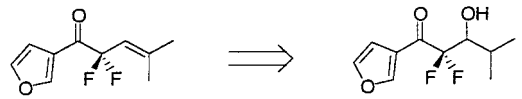


Table 2. One-Pot Aldol Reaction Promoted by a Catalytic Amount of $Yb(OTf)_3$

Entry	R^1	R^2	Aldol (% yield)[a,b]
1	CH_3		**3g** (43) + **3h** (19)[c]
2	Ph	Ph	**3a** (65)
3	Ph		**3c** (49)
4	Ph		**3e** (78)
5	Ph		**3i** (52)
6	Ph		**3j** (52)[d]
7	CH_3	C_8H_{17}	**3k** (51)[e]
8	CH_3		**3l**(53)[f]

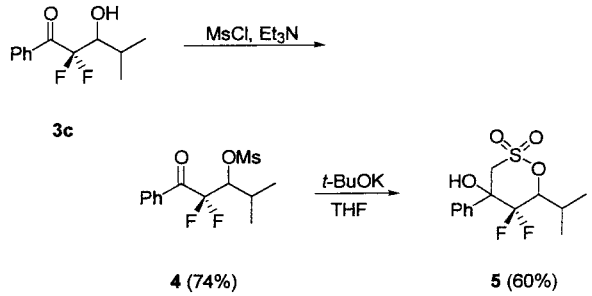
[a] Isolated yield. [b] Overall yield based on the starting acylsilane. [c] *O*-Silylated aldol. This reaction was carried out without fluoride workup. [d] 75/25 mixture of isomers. [e] Isolated as the hydrate. [f] 75/25 mixture of diastereomers.

Scheme 3



failed because of the destabilization of the intermediate carbocation. For example, **3c** did not undergo dehydration when treated with H_2SO_4 or H_3PO_4 in THF, CH_2Cl_2, or DMF even at reflux temperature. Compound **3c** was then converted into the corresponding sulfonic or phosphoric derivatives in order to attempt a β-elimination under basic conditions. No elimination reaction occurred when **3c** was reacted with thionyl chloride or phosphorus oxychloride in the presence of triethylamine whereas the corresponding mesylate **4** led to the sultone **5** under treatment with potassium *tert*-butoxide (Scheme 4). The deprotonation of the methanesulfonyl moiety and subsequent intramolecular addition to the carbonyl group proved to be more favorable than β-elimination. One can assume that the difluoromethylene unit stabilizes the quaternization of the adjacent carbon atom and prevents a retro-aldol process, thus explaining the formation of

Scheme 4



the kinetic product **5**. We anticipated that this side reaction could be avoided by performing the elimination reaction on the tosylate derivative. Indeed, β-elimination took place in the presence of DBU, but only 33% of the tosylate (NMR monitoring) was transformed after 8 h at reflux in toluene. The difluoroaldol **3c** was successfully dehydrated via its triflate derivative **6c** which underwent a mild β-elimination at room temperature in toluene using DBU as a base according to a reported procedure (Scheme 5).[21] One should notice, that because of the presence of fluorine atoms in α-position of the triflate, **6c** happened to be very stable, and it could be obtained in a very good yield after purification by silica gel chromatography. The conversion of **3c** into **7c** was effective even without isolation of the intermediate triflate, but replacement of dichloromethane by toluene was essential for the elimination step. Finally, the furan-derived aldol **3d** was subjected to this reaction sequence. Its preparation proved to be more efficient with $BF_3{\cdot}OEt_2$ than with $Yb(OTf)_3$ as the Lewis acid. It was converted in fair yield into the triflate **6d** whose β-elimination occurred in a good yield to give the difluoroegomaketone **7d** (Scheme 5).

Conclusion

Acylsilane + TFMTMS + aldehyde constitute an effective convergent three-component system for the synthesis of difluoroaldol via the key intermediate difluoroenoxysilane. The possibility of quantitatively generating the difluoroenoxysilane in dichloromethane, the effectiveness of ytterbium triflate used in a catalytic amount, and the one-pot character of this transformation are the main attractive features of this chemistry. The application of the above strategy to the synthesis of difluoroegomaketone is an illustration of the potential of this methodology toward the synthesis of elaborate fluorinated compounds.

Experimental Section[15]

Commercially available reagents were used as supplied. Tetrabutyl-*n*-ammonium difluorotriphenylstannate (DFTPS) was prepared according to the reported procedure.[22]

Warning. Care should be taken in the manipulation of the following fluorinated compounds, as they may be biochemically active. Their toxicological properties are unknown.

Acylsilanes Preparations. The acylsilanes **1a**[23] and **1b** were synthesized by the Brook and Corey method.[23,24]

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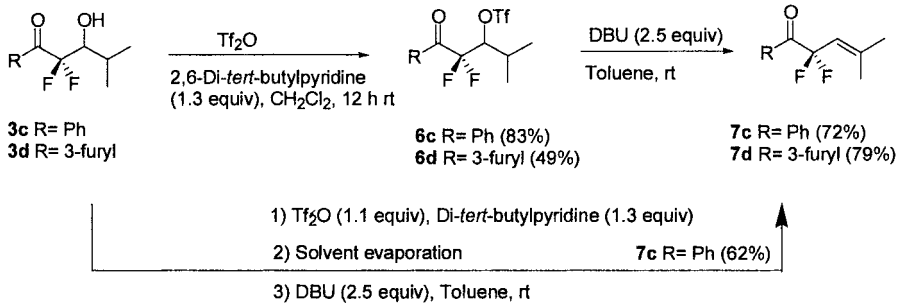
Scheme 5



3-Furoyltrimethylsilane (1b): yellow oil; flash chromatography (petroleum ether−CH_2Cl_2, 4:1); ^{1}H NMR δ 0.32 (s, 9H), 6.73 (d, $^3J_{HH}$ = 1.9 Hz, 1H), 7.41 (d, $^3J_{HH}$ = 1.9 Hz, 1H), 8.07 (s, 1H); ^{13}C NMR δ −2.13, 106.4, 129.2, 143.7, 148.2, 228.5; IR (neat) 1593, 1248, 1153 cm^{-1}; MS *m*/*z* 168 ($M^{+\bullet}$ + 1, 79), 167 (100), 125 (96), 107 (81). Anal. Calcd for $C_8H_{12}O_2Si$: C, 57.10, H, 7.19. Found: C, 57.22, H, 7.41.

Aldol Reaction. General Procedure

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

$TiCl_4$ Activation of the Aldehyde. To the solution of difluoroenoxysilane were added the aldehyde (1.8−2.2 mmol, 1.2−1.5 equiv) and $TiCl_4$ (1.8−2.2 mmol, 1.2−1.5 equiv) at −78 °C (see Table 1). After being stirred 24 h 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 and dried over $MgSO_4$, and the solvent was evaporated under reduced pressure. The crude product was purified by silica gel column chromatography.

BF_3·OEt_2 Activation of the Aldehyde. To the solution of difluoroenoxysilane were added the aldehyde (2.2 mmol, 1.5 equiv) and BF_3·OEt_2 (1.8 mmol, 1.2 equiv) at −30 °C. After being stirred 24 h 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 and dried over $MgSO_4$, and the solvent was evaporated under reduced pressure. The crude product was purified by silica gel column chromatography.

$Yb(OTf)_3$ Activation of the Aldehyde. To the solution of difluoroenoxysilane were added the aldehyde (1.8 mmol, 1.2 equiv) and $Yb(OTf)_3$ (0.15 mmol, 0.1 equiv) at room temperature. The reaction mixture was stirred 24 h at room temperature, and Bu_4NF·$3H_2O$ (1 equiv) or an aqueous solution of KF (6 mmol, 4 equiv, in 2 mL) was added. The mixture was then stirred for 3 h (Bu_4NF·$3H_2O$) or 48 h (KF), and a saturated $NaHCO_3$ solution (10 mL) was added. After extraction with CH_2Cl_2 (3 × 15 mL), the organic layer was washed with brine and dried over $MgSO_4$, and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography over silica gel.

2,2-Difluoro-3-hydroxy-1,3-diphenylpropan-1-one (3a):[11d] yellow oil; flash chromatography (petroleum ether−CH_2Cl_2, 1:1); ^{1}H NMR δ 3.10 (d, $^3J_{HH}$ = 5.0 Hz, 1H, OH), 5.34 (dt, $^3J_{HF}$ = 18.6 Hz, $^3J_{HF}$ = $^3J_{HH}$ = 5.0 Hz, 1H), 7.34−8.04 (m, 10H); ^{19}F NMR δ −106.0 (d, J_{AB} = 292.0 Hz, 1F), −116.8 (dd, J_{AB} = 292.0 Hz, $^3J_{FH}$ = 18.6 Hz, 1F); ^{13}C NMR δ 73.4 (dd, $^2J_{CF}$ = 27.6 Hz, $^2J_{CF}$ = 21.7 Hz), 116.0 (dd, J_{CF} = 263.8 Hz, J_{CF} = 258.0 Hz), 134.9, 134.5, 132.6, 130.2, 129.0, 128.6, 128.3, 128.1, 191.0 (t, $^2J_{CF}$ = 29.5 Hz); IR (neat) 3474, 3036, 1693 cm^{-1}. Anal. Calcd for $C_{15}H_{12}O_2F_2$: C, 68.70, H, 4.61. Found: C, 68.35, H, 6.63.

2,2-Difluoro-3-hydroxy-5-methyl-1-phenylhexan-1-one (3b): light yellow oil; flash chromatography (petroleum ether−CH_2Cl_2, 1:1); ^{1}H NMR δ 0.96 (d, $^3J_{HH}$ = 6.5 Hz, 3H), 1.01 (d, $^3J_{HH}$ = 6.5 Hz, 3H), 1.50 (ddt, J_{AB} = 14.1 Hz, $^3J_{HH}$ = 6.9 Hz, $^3J_{HH}$ = $^4J_{HF}$ = 2.3 Hz, 1H), 1.44 (m, 1H), 1.66 (ddd, J_{AB} = 14.1 Hz, $^3J_{HH}$ = 9.7 Hz, $^3J_{HH}$ = 4.2 Hz, 1H), 2.46 (m, 1H), 4.33 (ddd, $^3J_{HF}$ = 16.0 Hz, $^3J_{HH}$ = 9.7 Hz, $^3J_{HH}$ = 6.9 Hz, 1H), 7.51 (tm, $^3J_{HH}$ = 7.6 Hz, 2H), 7.66 (tm, $^3J_{HH}$ = 7.2 Hz, 1H), 8.11 (d, $^3J_{HH}$ = 8.4 Hz, 2H); ^{19}F NMR δ −108.5 (d, J_{AB} = 293.7 Hz, 1F), −117.5 (dd, J_{AB} = 293.7 Hz, $^3J_{FH}$ = 16.0 Hz, 1F); ^{13}C NMR δ 21.2, 23.5, 24.1, 37.6, 69.7 (t, $^2J_{CF}$ = 25.6 Hz), 116.8 (t, J_{CF} = 258.9 Hz), 128.9, 130.2, 132.4, 134.4, 190.7 (t, $^2J_{CF}$ = 30.5 Hz); IR (neat) 3452, 2957, 2926, 1697, 1116 cm^{-1}. Anal. Calcd for $C_{13}H_{16}O_2F_2$: C, 64.54, H, 6.66. Found: C, 64.37, H, 6.74.

2,2-Difluoro-3-hydroxy-4-methyl-1-phenylpentan-1-one (3c): light yellow oil; flash chromatography (petroleum ether−AcOEt, 9:1); ^{1}H NMR δ 1.07 (d, $^3J_{HH}$ = 6.1 Hz, 3H), 1.01 (d, $^3J_{HH}$ = 6.1 Hz, 3H), 2.16 (o, $^3J_{HH}$ = 6.1 Hz, 1H), 2.53 (d, $^3J_{HH}$ = 6.1 Hz, 1H), 4.07 (dt, $^3J_{HF}$ = 19.5 Hz, $^3J_{HH}$ = 6.1 Hz, 1H), 7.39−7.68 (m, 3H), 8.10 (d, $^3J_{HH}$ = 8.4 Hz, 2H); ^{19}F NMR δ −105.8 (d, J_{AB} = 289.9 Hz, 1F), −116.0 (dd, J_{AB} = 289.9 Hz, $^3J_{HF}$ = 19.5 Hz, 1F); ^{13}C NMR δ 17.1, 20.2, 28.3, 74.9 (dd, $^2J_{CF}$ = 26.6 Hz, $^2J_{CF}$ = 22.6 Hz), 117.6 (dd, J_{CF} = 258.9 Hz, J_{CF} = 268.8 Hz), 128.6, 130.1, 132.5, 134.4, 190.8 (t, $^2J_{CF}$ = 30.5 Hz); IR (neat) 3460, 2957, 1697 cm^{-1}; MS *m*/*z* 228 (M^+, 10), 208 (M^+-HF, 60), 192 (51), 165 (100). Anal. Calcd for $C_{12}H_{14}O_2F_2$: C, 63.15, H, 6.18. Found: C, 63.55, H, 6.57.

2,2-Difluoro-1-(3-furyl)-3-hydroxy-4-methylpentan-1-one (3d): light yellow oil; flash chromatography (petroleum ether−AcOEt, 9:1); ^{1}H NMR δ 1.06 (d, $^3J_{HH}$ = 5.9 Hz, 6H), 1.63 (m, 1H), 2.12 (m, 1H), 3.99 (ddd, $^3J_{HF}$ = 19.5 Hz, $^3J_{HH}$ = 6.9 Hz, $^3J_{HF}$ = 4.9 Hz, 1H), 6.88 (s, 1H), 7.47 (s, 1H), 8.26 (s, 1H); ^{19}F NMR δ −108.8 (dd, J_{AB} = 274.7 Hz, $^3J_{HF}$ = 4.9 Hz, 1F), −119.3 (dd, J_{AB} = 274.7 Hz, $^3J_{HF}$ = 19.5 Hz, 1F); ^{13}C NMR δ 17.0, 19.9, 28.3, 77.8 (t, $^2J_{CF}$ = 23.6 Hz), 109.2, 117.4 (dd, J_{CF} = 259.9 Hz, J_{CF} = 256.0 Hz), 122.6, 143.9, 150.6 (dd, $^3J_{CF}$ = 11.8 Hz, $^3J_{CF}$ = 5.9 Hz), 186.2 (t, $^2J_{CF}$ = 33.5 Hz); IR (neat) 3460, 2966, 2936, 1691 cm^{-1}. Anal. Calcd for $C_{10}H_{12}O_3F_2$: C, 55.05, H, 5.54. Found: C, 55.22, H, 5.86.

2,2-Difluoro-3-hydroxy-5-methyl-1-phenylhex-4-en-1-one (3e): light yellow oil; flash chromatography (petroleum ether−CH_2Cl_2, 1:1); ^{1}H NMR δ 1.73 (s, 3H), 2.00 (s, 3H), 2.50 (m, 1H), 4.97 (dddd, $^3J_{HF}$ = 15.1 Hz, $^3J_{HF}$ = 7.9 Hz, $^3J_{HH}$ = 8.6 Hz, $^3J_{HH}$ = 6.2 Hz, 1H), 5.36 (dm, $^3J_{HH}$ = 8.6 Hz, 1H), 7.49 (tm, $^3J_{HH}$ = 7.6 Hz, 2H), 7.64 (tm, $^3J_{HH}$ = 7.6 Hz, 1H), 8.09 (dm, $^3J_{HH}$ = 7.6 Hz, 2H); ^{19}F NMR δ −108.5 (dd, J_{AB} = 286.1 Hz, $^3J_{HF}$ = 7.9 Hz, 1F), −115.3 (dd, J_{AB} = 286.1 Hz, $^3J_{HF}$ = 15.1 Hz, 1F); ^{13}C NMR δ 18.5, 25.9, 68.8 (t, $^2J_{CF}$ = 26.6 Hz), 116.7 (dd, J_{CF} = 256.0 Hz, J_{CF} = 261.9 Hz), 118.2, 128.6, 130.1, 132.7, 134.3, 141.7, 190.5 (t, $^2J_{CF}$ = 29.5 Hz); IR (neat) 3427, 1697, 1450 cm^{-1}; MS *m*/*z* 241 (M^+, 10), 205 (50), 156 (42); HRMS calcd for $C_{13}H_{15}O_2F_2$ 240.0961, found 240.0927.

5-Chloro-2,2-difluoro-5-methyl-1-phenylhex-3-en-1-one (3f): colorless oil; flash chromatography (petroleum ether−CH_2Cl_2, 4:1); ^{1}H NMR δ 1.73 (s, 6H), 6.09 (dt, $^3J_{HH}$ = 16.0 Hz, $^3J_{HF}$ = 11.1 Hz, 1H), 6.48 (dt, $^3J_{HH}$ = 16.0 Hz, $^4J_{HF}$ = 2.5 Hz, 1H), 7.51 (tm, $^3J_{HH}$ = 7.4 Hz, 2H), 7.65 (tm, $^3J_{HH}$ = 7.4 Hz, 1H), 8.08 (d, $^3J_{HH}$ = 7.4 Hz, 2H); ^{19}F NMR δ −98.5 (d, $^3J_{HF}$ = 11.1 Hz, 2F); ^{13}C NMR δ 31.6, 65.7, 115.6 (t, J_{CF} = 250.0 Hz), 120.0 (t, $^2J_{CF}$ = 24.6 Hz), 128.7, 130.1, 131.9, 134.3, 143.8 (t, $^3J_{CF}$ = 8.9 Hz), 188.6 (t, $^2J_{CF}$ = 31.5 Hz); IR (neat) 1705, 1259

cm^{-1}. Anal. Calcd for $C_{13}H_{13}OF_2Cl$: C, 60.36, H, 5.06. Found: C, 60.58, H, 4.95.

3,3-Difluoro-4-hydroxy-4-(2-naphthyl)butan-2-one (3g): white solid; flash chromatography (petroleum ether−AcOEt, 9:1); mp 108 °C; ^{1}H NMR δ 2.29 (t, $^4J_{HF}$ = 1.1 Hz, 3H), 2.65 (m, 1H), 5.31 (dd, $^3J_{HF}$ = 15.9 Hz, $^3J_{HF}$ = 7.5 Hz, 1H), 7.47−7.58 (m, 3H), 7.81−7.92 (m, 4H); ^{19}F NMR δ −113.0 (dd, J_{AB} = 270.3 Hz, $^3J_{HF}$ = 7.5 Hz, 1F), −122.2 (dd, J_{AB} = 270.3 Hz, $^3J_{HF}$ = 15.9 Hz, 1F); ^{13}C NMR δ 25.7, 73.2 (dd, $^2J_{CF}$ = 28.5 Hz, $^2J_{CF}$ = 24.6 Hz), 114.6 (dd, J_{CF} = 261.8 Hz, J_{CF} = 255.9 Hz), 124.9, 126.4, 126.7, 127.5, 127.7, 128.2, 132.1, 132.9, 133.6, 200.1 (dd, $^2J_{CF}$ = 32.5 Hz, $^2J_{CF}$ = 27.5 Hz); IR (KBr) 3462, 1736, 1601, 1111 cm^{-1}; MS *m*/*z* 250 (M$^+$, 24), 157 (90), 129 (100). Anal. Calcd for $C_{14}H_{12}O_2F_2$: C, 67.20, H, 4.83. Found: C, 67.04, H, 4.83.

3,3-Difluoro-4-(2-naphthyl)-4-trimethylsilyloxybutan-2-one (3h): white solid; flash chromatography (petroleum ether−AcOEt, 95:5); mp 69 °C; ^{1}H NMR δ 0.07 (s, 9H), 2.37 (d, $^4J_{HF}$ = 2.7 Hz, 3H), 5.25 (dd, $^3J_{HF}$ = 17.9 Hz, $^3J_{HF}$ = 6.5 Hz, 1H), 7.50−7.59 (m, 3H), 7.85−7.88 (m, 4H); ^{19}F NMR δ −111.2 (dd, J_{AB} = 255.5 Hz, $^3J_{HF}$ = 6.5 Hz, 1F), −124.7 (dd, J_{AB} = 255.5 Hz, $^3J_{HF}$ = 17.9 Hz, 1F); ^{13}C NMR δ −0.2, 26.6, 74.2 (dd, $^2J_{CF}$ = 31.5 Hz, $^2J_{CF}$ = 23.6 Hz), 115.2 (dd, J_{CF} = 261.1 Hz, J_{CF} = 253.1 Hz), 125.3, 126.3, 126.5, 127.7, 127.8, 127.9, 128.2, 132.8, 133.2, 133.6, 200.9 (dd, $^2J_{CF}$ = 33.2 Hz, $^2J_{CF}$ = 24.0 Hz); IR (KBr) 2959, 1738, 1253 cm^{-1}; MS *m*/*z* 322 (M$^+$, 20), 250 (15), 229 (100); HRMS calcd for $C_{17}H_2O_2F_2Si$ 322.1200, found 322.1188.

2,2-Difluoro-3-hydroxy-1-phenylpent-4-en-1-one (3i): colorless oil; flash chromatography (petroleum ether−CH_2Cl_2, 1:1); ^{1}H NMR δ 2.75 (m, 1H), 4.78 (dt, $^3J_{HF}$ = 15.6 Hz, $^3J_{HF}$ = $^3J_{HH}$ = 5.7 Hz, 1H), 5.45 (dd, $^3J_{HH}$ = 10.6 Hz, $^4J_{HH}$ = 1.4 Hz, 1H), 5.52 (d, $^3J_{HH}$ = 17.2 Hz, 1H), 6.03 (ddd, $^3J_{HH}$ = 17.2 Hz, $^3J_{HH}$ = 10.6 Hz, $^3J_{HH}$ = 5.7 Hz, 1H), 7.50 (t, $^3J_{HH}$ = 7.9 Hz, 2H), 7.65 (t, $^3J_{HH}$ = 7.9 Hz, 1H), 8.11 (d, $^3J_{HH}$ = 7.9 Hz, 2H); ^{19}F NMR δ −107.1 (dd, J_{AB} = 293.7 Hz, $^3J_{HF}$ = 5.7 Hz, 1F), −115.6 (dd, J_{AB} = 293.7 Hz, $^3J_{HF}$ = 15.6 Hz, 1F); ^{13}C NMR δ 72.5 (dd, $^2J_{CF}$ = 27.6 Hz, $^2J_{CF}$ = 25.6 Hz), 115.8 (dd, J_{CF} = 261.8 Hz, J_{CF} = 257.9 Hz), 120.4, 128.7, 130.2 (t, $^3J_{CF}$ = 3.9 Hz), 131.2, 134.6, 190.3 (t, $^2J_{CF}$ = 29.5 Hz); IR (neat) 3439, 1699, 1599 cm^{-1}; MS *m*/*z* 213 (M$^+$, 5), 156 (43), 105 (100).

2,2-Difluoro-3-hydroxy-5,9-dimethyl-1-phenyldeca-4,8-dien-1-one (3j) (75:25 isomers mixture): light yellow oil; flash chromatography (petroleum ether−ethyl acetate, 93:7); ^{1}H NMR *(major isomer)* δ 1.59 (s, 3H), 1.66 (s, 3H), 1.71 (d, $^4J_{HH}$ = 1.1 Hz, 3H), 2.07 (m, 4H), 2.40 (d, $^3J_{HH}$ = 5.7 Hz, 1H), 5.00 (m, 1H), 5.05 (m, 1H), 5.34 (d, $^3J_{HH}$ = 9.1 Hz, 1H), 7.49 (tm, $^3J_{HH}$ = 7.6 Hz, 2H), 7.64 (tm, $^3J_{HH}$ = 7.6 Hz, 1H), 8.10 (d, $^3J_{HH}$ = 7.6 Hz, 2H); *(minor isomer)* δ 1.60 (s, 3H), 1.68 (s, 3H), 1.80 (d, $^4J_{HH}$ = 1.1 Hz, 3H), 2.09 (m, 4H), 2.33 (d, $^3J_{HH}$ = 5.2 Hz, 1H), 5.00 (m, 1H), 5.05 (m, 1H), 5.40 (d, $^3J_{HH}$ = 8.7 Hz, 1H), 7.49 (tm, $^3J_{HH}$ = 7.6 Hz, 2H), 7.64 (tm, $^3J_{HH}$ = 7.6 Hz, 1H), 8.10 (d, $^3J_{HH}$ = 7.6 Hz, 2H); ^{19}F NMR *(major isomer)* δ −108.8 (ddd, J_{AB} = 286.1 Hz, $^3J_{HF}$ = 22.9 Hz, $^4J_{HF}$ = 7.6 Hz, 1F), −115.0 (dd, J_{AB} = 286.1 Hz, $^3J_{HF}$ = 15.2 Hz, 1F); *(minor isomer)* δ −107.4 (dm, J_{AB} = 286.1 Hz, 1F), −116.1 (dd, J_{AB} = 286.1 Hz, $^3J_{HF}$ = 17.2 Hz, 1F); ^{13}C NMR *(major isomer)* δ 17.0, 17.6, 25.5, 26.0, 39.6, 68.7 (t, $^2J_{CF}$ = 25.6 Hz), 116.8 (dd, J_{CF} = 259.9 Hz, J_{CF} = 256.0 Hz), 117.9, 123.4, 128.6, 130.0, 131.9, 132.6, 134.3, 145.0, 191.0 (t, $^2J_{CF}$ = 31.5 Hz); *(minor isomer)* δ 17.0, 17.6, 25.6, 26.3, 40.5, 68.6 (t, $^2J_{CF}$ = 25.4 Hz), 116.6 (dd, J_{CF} = 265.8 Hz, J_{CF} = 261.9 Hz), 118.4, 123.4, 128.6, 130.0, 132.4, 132.9, 134.3, 145.4, 190.5 (t, $^2J_{CF}$ = 29.5 Hz); IR (neat) 3418, 2966, 2916, 1699 cm^{-1}; MS *m*/*z* 308 (M$^+$, 25), 291 (99), 105 (100); HRMS calcd for $C_{18}H_{22}O_2F_2$ 308.1585, found 308.1570.

3,3-Difluoro-dodecane-2,2,4-triol (3k): white solid; flash chromatography (petroleum ether−AcOEt, 9:1); mp 42 °C; ^{1}H NMR δ 0.87 (t, $^3J_{HH}$ = 6.5 Hz, 3H), 1.14−1.45 (m, 12 H), 1.52 (s, 1H), 2.42 (m, 5H), 3.99 (ddd, $^3J_{HF}$ = 22.9 Hz, $^3J_{HH}$ = 8.4 Hz, $^3J_{HH}$ = 4.2 Hz, 1H), 5.15 (m, 2H); ^{19}F NMR δ −129.2 (d, J_{AB} = 249.8 Hz, 1F), −131.4 (dd, J_{AB} = 249.8, $^3J_{HH}$ = 22.9 Hz, 1F); ^{13}C NMR δ 14.1, 22.6, 24.1, 25.1, 29.3, 29.4, 29.5, 31.8, 33.7, 73.8 (dd, $^2J_{CF}$ = 29.5 Hz, $^2J_{CF}$ = 23.6 Hz), 95.2 (dd, $^2J_{CF}$ = 33.5 Hz, $^2J_{CF}$ = 25.6 Hz), 113.9 (t, J_{CF} = 253.9 Hz); IR (KBr) 3935, 2918, 1471, 1142 cm^{-1}; MS *m*/*z* 250 (18), 229 (58), 157 (93), 129 (100).

(1R)-4-(6,6-Dimethylbicyclo[3.1.1]hept-2-en-2-yl)-3,3-difluoro-4-hydroxybutan-2-one (3l) (75:25 mixture of diastereomers): colorless oil; flash chromatography (petroleum ether−ethyl acetate, 92:8); ^{1}H NMR δ 0.85 (s, 3H), 1.34 (s, 3H), 1.97−2.49 (m, 7H), 2.33 (d, $^4J_{HF}$ = 3.4 Hz, 3H *minor isomer*), 2.38 (d, $^4J_{HF}$ = 2.3 Hz, 3H *major isomer*), 4.49 (dd, $^3J_{HF}$ = 18.3 Hz, $^3J_{HF}$ = 7.6 Hz 1H), 5.70 (m, 1H); ^{19}F NMR (*major isomer*) δ −112.3 (dd, J_{FF} = 270.8 Hz, $^3J_{HF}$ = 7.6 Hz, 1F), −122.8 (dd, J_{FF} = 270.8 Hz, $^3J_{HF}$ = 18.3 Hz, 1F); (*minor isomer*) δ −110.9 (d, J_{FF} = 267.0 Hz, 1F), −123.8 (dd, J_{FF} = 267.0, $^3J_{HF}$ = 15.3 Hz, 1F); ^{13}C NMR (*major isomer*) δ 21.1, 25.5, 26.0, 31.5, 31.7, 40.6, 42.6, 73.1 (dd, $^2J_{C-F}$ = 27.6 Hz, $^2J_{C-F}$ = 23.6 Hz), 115.3 (dd, J_{C-F} = 261.8 Hz, J_{C-F} = 253.9 Hz), 124.6, 142.3, 200.1 (dd, $^2J_{CF}$ = 27.3 Hz, $^2J_{CF}$ = 33.5 Hz); (*minor isomer*) δ 21.3, 25.8, 26.1, 31.5, 31.7, 40.3, 42.6, 73.4 (dd, $^2J_{C-F}$ = 29.5 Hz, $^2J_{C-F}$ = 26.6 Hz), 115.3 (dd, J_{C-F} = 261.8 Hz, J_{C-F} = 253.9 Hz), 124.7, 142.5, 200.1 (dd, $^2J_{C-F}$ = 33.6 Hz, $^2J_{C-F}$ = 27.1 Hz); IR (neat) 3449, 2922, 1743 cm^{-1}; MS *m*/*z* 244 (M$^+$, 8), 227 (25), 121 (23); 107 (100); HRMS calcd for $C_{13}H_{18}O_2F_2$ 244.1275, found 244.1294.

Dehydration of Aldol Compounds

2,2-Difluoro-3-methanesulfonyloxy-4-methyl-1-phenylpentan-1-one (4). Triethylamine (0.55 mL, 3.6 mmol, 6 equiv) and methanesulfonyl chloride (0.15 mL, 2.0 mmol, 3 equiv) were added to a solution of **3c** (0.15 g, 0.6 mmol) in CH_2Cl_2 (3 mL) at 0°. The mixture was stirred overnight, and water (10 mL) was added. After extraction with CH_2Cl_2 (3 × 15 mL), the organic layer was washed with brine and dried over $MgSO_4$, and the solvent was evaporated under reduced pressure, giving **4** (0.150 g, 74%) as a red liquid. ^{1}H NMR δ 1.09 (d, $^3J_{HH}$ = 6.1 Hz, 6H), 2.19−2.27 (m, 1H), 3.08 (s, 3H), 5.23 (ddd, $^3J_{HF}$ = 14.9 Hz, $^3J_{HF}$ = 10.9 Hz, $^3J_{HH}$ = 4.0 Hz, 1H), 7.51−7.72 (m, 3H), 8.10 (d, $^3J_{HH}$ = 8.2 Hz, 2H); ^{19}F NMR δ −103.4 (dd, J_{AB} = 288.0 Hz, $^3J_{HF}$ = 10.9 Hz, 1F), −110.4 (dd, J_{AB} = 288.0 Hz, $^3J_{HH}$ = 14.9 Hz, 1F); ^{13}C NMR δ 16.8, 20.1, 28.4, 38.9, 82.5 (dd, $^2J_{CF}$ = 23.6 Hz, $^2J_{CF}$ = 19.7 Hz), 116.2 (t, J_{CF} = 259.8 Hz), 129.0, 130.0 (t, $^3J_{CF}$ = 3.9 Hz), 131.8, 134.9, 188.3 (t, $^2J_{CF}$ = 31.5 Hz); MS *m*/*z* 201 (M$^+$-105, 65), 105 (100).

3,3-Difluoro-2-hydroxy-2-phenyl-4-isopropylbutan-1,4-sultone (5). To a solution of mesylate **4** (0.15 g, 0.5 mmol) in THF (3 mL) was added *t*-BuOK (0.07 g, 0.6 mmol, 1.2 equiv) at room temperature. The mixture was stirred 24 h, and water (5 mL) was added. After extraction with Et_2O (3 × 15 mL), the organic layer was washed with brine and dried over $MgSO_4$, and the solvent was evaporated under reduced pressure. Purification by flash chromatography (petroleum ether−CH_2Cl_2, 3:2) gave **5** (0.085 g, 60%) as a solid; mp 197 °C; ^{1}H NMR δ 1.14 (m, 6H), 1.56 (s, 1H) 2.39 (m, 1H), 3.46 (d, J_{AB} = 14.5 Hz, 1H), 4.14 (dm, J_{AB} = 14.5 Hz, 1H), 4.92 (dd, $^3J_{HF}$ = 23.0 Hz, $^3J_{HH}$ = 4.8 Hz, 1H), 7.43 (massif, 3H), 7.63 (massif, 2H); ^{19}F NMR δ −128.1 (d, J_{AB} = 265.1 Hz, 1F), 123.6 (dd, J_{AB} = 265.1 Hz, $^3J_{FH}$ = 23.0 Hz, 1F)); ^{13}C NMR δ 17.4 (d, $^4J_{CF}$ = 3.9 Hz), 19.8 (d, $^4J_{CF}$ = 3.9 Hz), 27.3, 54.2, 74.0 (t, $^2J_{CF}$ = 27.6 Hz), 83.0 (dd, $^2J_{CF}$ = 35.4 Hz, $^2J_{CF}$ = 24.6 Hz), 116.2 (t, J_{CF} = 258.8 Hz), 126.5, 128.5, 129.3, 135.2; IR (KBr) 3462, 2922, 1441, 1340 cm^{-1}; MS *m*/*z* 201 (M$^+$ − 105, 72), 105 (100). Anal. Calcd for $C_{13}H_{16}O_4F_2S$: C, 50.97, H, 5.26. Found: C, 51.24, H, 5.03.

2,2-Difluoro-3-trifluoromethanesulfonyloxy-4-methyl-1-phenylpentan-1-one (6c). To a solution of aldol **3c** (0.255 g, 1.1 mmol) in CH_2Cl_2 (5 mL) at 0 °C under argon were added 2,6-di-*tert*-butylpyridine (0.33 mL, 1.3 equiv) and triflic anhydride (0.21 mL, 1.1 equiv). The mixture was stirred overnight at room temperature. After addition of a saturated NH_4Cl solution (10 mL), the solution was extracted with CH_2Cl_2 (3 × 15 mL). The organic layer was washed with brine and dried over $MgSO_4$, and the solvent was evaporated under reduced pressure. Purification by flash chromatography (petroleum ether−CH_2Cl_2, 4:1) gave **6c** (0.335 g, 83%). Oil. ^{1}H NMR δ 1.13 (d, $^3J_{HH}$ = 6.9 Hz, 3H), 1.17 (d, $^3J_{HH}$ = 7.2 Hz, 3H), 2.35 (m, 1H), 5.49 (ddd, $^3J_{HF}$ = 17.5 Hz, $^3J_{HH}$ = 6.9 Hz, $^3J_{HF}$ = 3.4 Hz, 1H), 7.52 (m, 2H), 7.70 (t, $^3J_{HH}$ = 7.5 Hz, 1H); 8.16 (d, $^3J_{HH}$ = 7.5 Hz, 2H); ^{19}F NMR δ −74.1 (s, 3F), −100.4 (d, $^2J_{FF}$ = 298

Hz, 1F), −112.6 (dd, $^2J_{FF}$ = 298 Hz, $^3J_{HF}$ = 17.5 Hz, 1F); ^{13}C NMR δ 16.4, 20.1, 28.6, 87.5 (dd, $^2J_{CF}$ = 23.6 Hz, $^2J_{CF}$ = 19.7 Hz), 114.8 (t, J_{CF} = 290.0 Hz), 118.5 (q, J_{CF} = 318.0 Hz), 129.0, 130.1, 131.3, 135.9, 187.4 (t, $^2J_{CF}$ = 30.5 Hz).

2,2-Difluoro-3-trifluoromethanesulfonyloxy-1-(3-furanyl)-4-methylpentan-1-one (6d). Following the same procedure than for the aldol **3c**, **3d** (0.526 g, 2.4 mmol) gave **6d** (0.409 g, 49%) as a colorless oil after purification by flash chromatography (petroleum ether−CH_2Cl_2, 9:1). ^{1}H NMR δ 0.99 (d, $^3J_{HH}$ = 5.7 Hz, 3H), 1.00 (d, $^3J_{HH}$ = 6.9 Hz, 3H), 2.19 (m, 1H), 5.22 (ddd, $^3J_{HF}$ = 16.4 Hz, $^3J_{HF}$ = 7.6 Hz, $^3J_{HH}$ = 3.8 Hz, 1H), 6.80 (s, 1H), 7.43 (s, 1H), 8.22 (s, 1H); ^{19}F NMR δ −74.4 (s, 3F), −104.1 (dd, J_{FF} = 282.0 Hz, $^3J_{HF}$ = 7.6 Hz, 1F), −115.7 (dd, J_{FF} = 282.0 Hz, $^3J_{HF}$ = 16.4 Hz, 1F); ^{13}C NMR δ 16.4, 19.7, 28.4, 87.4 (dd, $^2J_{CF}$ = 23.6 Hz, $^2J_{CF}$ = 20.7 Hz), 109.0, 114.5 (dd, J_{CF} = 263.0 Hz, J_{CF} = 259.0 Hz), 118.5 (q, J_{CF} = 320 Hz), 144.4, 150.6, 182.6 (t, $^2J_{CF}$ = 29.5 Hz); IR (neat) 3148, 2986, 1693, 1215 cm^{-1}; MS (CI$^+$) *m*/*z* 368 (M + 18, 45), 200 (100), 183 (84), 165 (71).

2,2-Difluoro-4-methyl-1-phenylpent-3-en-1-one (7c). To a solution of triflate **6c** (0.335 g, 0.9 mmol) in toluene (3 mL) was added DBU (0.34 mL, 2.3 mmol, 2.5 equiv) under argon. The mixture was stirred 4 h at room temperature. After addition of a saturated NH_4Cl solution (50 mL), the solution was extracted with CH_2Cl_2 (3 × 50 mL). The organic layer was washed with brine and dried over $MgSO_4$, and the solvent was evaporated under reduced pressure. Purification by flash chromatography (petroleum ether−CH_2Cl_2, 9:1) gave **7c** (0.140 g, 72%) as a colorless liquid. ^{1}H NMR δ 1.83 (m, 6H), 5.66 (tm, $^3J_{HF}$ = 13.3 Hz, 1H), 7.49 (m, 2H), 7.59 (m, 1H), 8.05 (d, $^3J_{HH}$ = 7.6 Hz, 2H); ^{19}F NMR δ −93.1 (d, $^3J_{HF}$ = 13.3 Hz); ^{13}C NMR δ 19.3, 26.6, 115.9 (t, J_{CF} = 249.0 Hz), 117.7 (t, $^2J_{CF}$ = 26.0 Hz), 128.2, 130.0, 132.0, 134.0, 147.2 (t, $^3J_{CF}$ = 7.7 Hz), 188.8 (t, $^2J_{CF}$ = 31.5 Hz); IR (neat), 2922, 1705, 1441 cm^{-1}. Anal. Calcd for $C_{12}H_{12}OF_2$: C, 68.56, H, 5.75. Found: C, 68.67, H, 6.03.

2,2-Difluoro-1-(3-furanyl)-4-methylpent-3-en-1-one (7d). Following the same procedure than for the triflate **6c**, **6d** (0.368 g, 1.0 mmol) gave **7d** (0.166 g, 79%) as a colorless solid after purification by flash chromatography (petroleum ether−CH_2Cl_2, 4:1). mp 42 °C; ^{1}H NMR δ 1.75 (s, 3H), 1.76 (s, 3H), 5.43 (tm, $^3J_{HF}$ = 15.2 Hz, 1H), 6.76 (s, 1H), 7.38 (s, 1H), 8.08 (s, 1H); ^{19}F NMR δ −96.4 (d, $^3J_{FH}$ = 15.2 Hz); ^{13}C NMR δ 19.3, 26.5, 109.4, 115.7 (t, J_{CF} = 248.7 Hz), 116.2 (t, $^2J_{CF}$ = 27.5 Hz), 122.0, 143.9, 147.7 (t, $^3J_{CF}$ = 7.9 Hz), 149.8, 184.2 (t, $^2J_{CF}$ = 35.5 Hz); IR (KBr) 3148, 2986, 2936, 1693 cm^{-1}; MS *m*/*z* 200 (M$^+$, 50), 181 (10), 149 (15), 105 (100). Anal. Calcd for $C_{10}H_{10}O_2F_2$: C, 60.00, H, 5.04. Found: C, 60.14, H, 5.15.

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