Pergamon

Tetrahedron 54 (1998) 5939–5948

TETRAHEDRON

Mixed Organofluorine-Organosilicon Chemistry. 8. One-pot Synthesis of 2,2-Difluoro-1,5 Diketones from Acylsilanes, Trifluoromethyltrimethylsilane and Enones, and their Annulation Reaction

Olivier Lefebvre, Thierry Brigaud and Charles Portella*

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

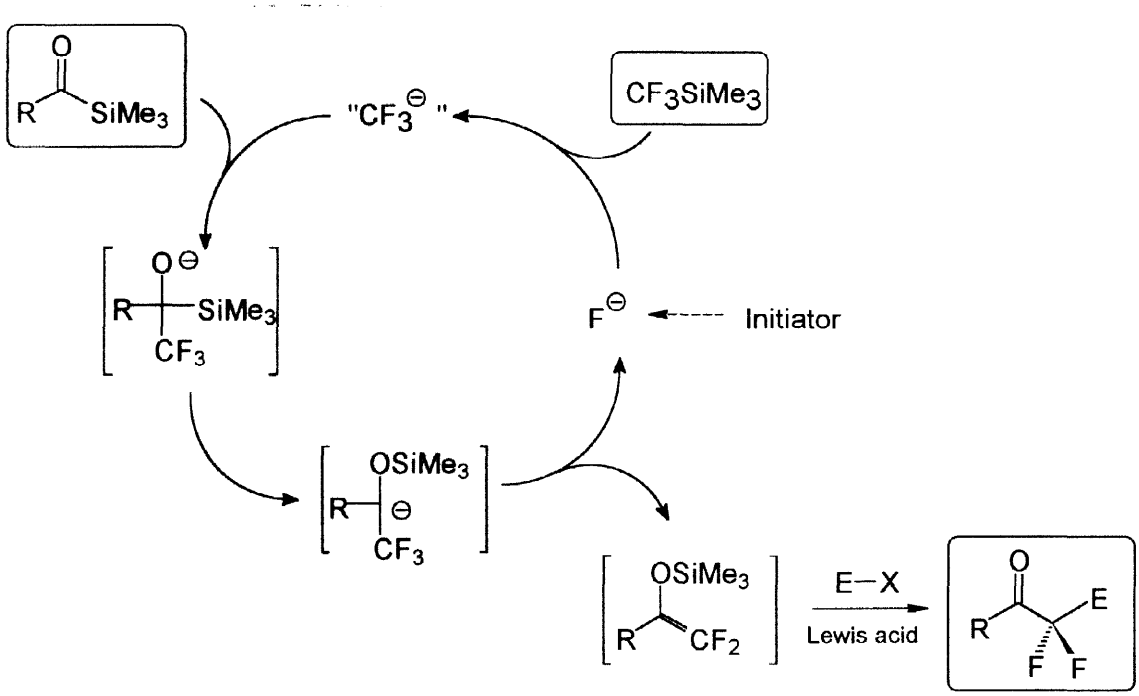
Received 19 December 1997; accepted 10 March 1998

Abstract : We describe the synthesis of 2,2-difluoro-1,5-diketones in a one-pot procedure from an acylsilane and trifluoromethyltrimethylsilane, via reaction of difluoroenoxysilanes and enones under electrophilic activation. These diketones are interesting building blocks for the synthesis of *gem*-difluoro enones or substituted fluorophenols, depending on the annulation conditions. The annulation proceeds with complete regioselectivity controlled by the fluorine substitution.

Difluoroenoxysilanes are excellent building blocks for the synthesis of *gem*-difluorinated compounds. They were first prepared from chlorodifluoromethylketones via the corresponding zinc enolates.[1] Another interesting approach used acylsilanes as starting material and their ability to rearrange (Brook rearrangement) under nucleophilic attack. Rather than the addition of an organometallic reagent to trifluoroacetyltriphenylsilane, which requires a silyllithium reagent for its synthesis,[2] we have developed an effective methodology for the preparation of difluoroenoxysilanes using the condensation of trifluoromethyltrimethylsilane (TFMTMS) with non fluorinated acylsilanes under catalytic fluoride activation.[3] The possibility of performing this reaction in a non-basic solvent such as methylene chloride allows the one-pot synthesis of difluoro derivatives by simple addition of an electrophilic substrate and an activating Lewis acid to the reaction medium. The overall process, depicted in Scheme 1, can be viewed as a very convergent synthesis of *gem*-difluoro compounds from a three component system, where the difluoromethylene group comes from TFMTMS, still known as one of the best sources of nucleophilic trifluoromethyl group.[4]

e-mail : charles.portella@univ-reims.fr ; fax : 33 (0)3 26 05 31 66

0040-4020/98/$19.00
PII: S0040-4020(98)00224-5

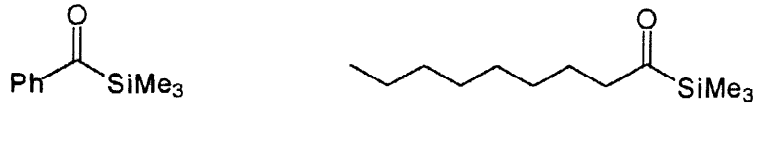


Scheme 1

Our preliminary accounts demonstrated the strategy by the *in situ* preparation of difluoroenoxysilanes and their subsequent trapping in alkylation and Mukaiyama aldol reactions[3] or in glycosylation reactions,[5] leading to the corresponding α,α-difluoroketones, α,α-difluoro-β-ketols or *C*-difluoro glycosides, respectively. We report in this paper the extension of this methodology to the synthesis of 2,2-difluoro-1,5-diketones by trapping of the enoxysilane by enones. We also describe the application of these diketones to the regioselective synthesis of α,α- or γ,γ-difluorocyclohexenones and to o- or p-fluorophenols, by subsequent annulation reactions.

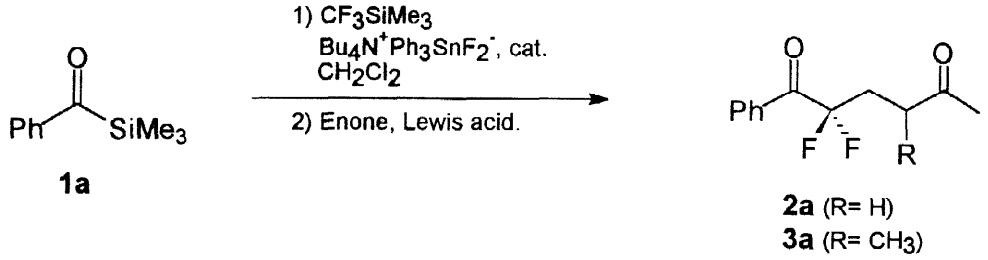
RESULTS AND DISCUSSION.

The difluoroenoxysilane was prepared according to the previously reported procedure, [3] by addition of a catalytic amount of tetrabutylammonium difluorotriphenylstannate (4%) to a solution of the acylsilane and TFMTMS in methylene chloride, at 0°C. After completion of the reaction (GC monitoring), the enone and then the Lewis acid were added to the reaction mixture at a temperature and with a stoichiometry which depended on the nature of the Lewis acid. Benzoyltrimethylsilane **1a** and nonanoyltrimethylsilane **1b** (Chart 1) were used as representatives of non-enolizable and enolizable acylsilanes. Conjugate additions to three enones, methyl vinyl ketone (MVK), 3-methylbut-3-en-2-one and cyclohex-2-enone were considered.



1a **1b**

Chart 1



1a

2a (R= H)
3a (R= CH_3)

Scheme 2

Table 1. Reaction with difluoroenoxysilane derived from benzoylsilane

Entry	eq. Enone	Reaction conditions	Yield (%)[a,b]
1	1.5	$TiCl_4$ (1.5 eq), -78°C	**2a** 30
2	1.5	$TiCl_4$ (1.8 eq), -78°C	**3a** 41
3	2	$BiCl_3$ (0.1eq) + ZnI_2 (0.15 eq), rt	**2a** 38
4	1.1	$BF_3.OEt_2$ (0.8 eq), menthol (1.1 eq), -78°C to rt	**2a** 60
5	2	Yb(OTf)$_3$ (0.03 eq), rt	**2a** 67

a) Pure isolated diketone. b)Overall yield based on acylsilane.

We first examined the Michael reaction conditions using benzoyltrimethylsilane, methyl vinyl ketone (MVK) or its α-methyl analog as models. The results are reported in Scheme 2 and Table 1. The Mukaiyama conditions[6] gave low yields (entry 1 and 2). The intermediate difluoroenoxysilane is a poor nucleophile owing to the fluorine atoms, and polymerization of the enone competes in the presence of a strong Lewis acid. Increasing the amount of reagents or the reaction time did not significantly improve the results. A soft Lewis acid such as bismuth trichloride, recently reported by Dubac's group as an effective catalyst for reaction of enoxysilanes with enones, especially after halogen exchange with an iodide salt,[7] did not prove to be well adapted to reactions of our difluoroenoxysilanes (entry 3). Duhamel *et al.* reported a dramatic improvement of Michael addition with enoxysilanes by adding one equivalent of a protic additive to the enone and using boron trifluoride etherate as Lewis acid.[8] Indeed, a better yield was obtained when one equivalent of menthol and 0.8 equivalent of $BF_3.OEt_2$ were added to the mixture of reactants (entry 4). According to recent reports from

Kobayashi *et al.*, lanthanide triflates are effective and versatile electrophilic activators for various reactions,[9] including Michael reactions. Such conditions gave the best results (entry 5): the reaction worked with only a catalytic amount of ytterbium triflate and is conveniently carried out at room temperature. The only drawback of these conditions is a longer reaction time, and the reaction still needs a two fold excess of enone to counter its polymerization.

The latter conditions were chosen as a general procedure for the one-pot synthesis of 2,2-difluoro-1,5-diketones. Good yields of diketones were obtained, taking into account that these yields refer to the overall process and are based on the starting acylsilanes. The reaction seems to be general working with both acylsilane and aroylsilane and with various enones including those with β- substituents such as cyclohexen-2-one to give the respective difluoro-1,5-diketones **2** and **4** (Chart 2). In contrast 1,2-addition occurred with enals (Scheme 3)[10] as has previously been reported for reactions of difluoroenolethers[11] and difluoroenolates.[12]

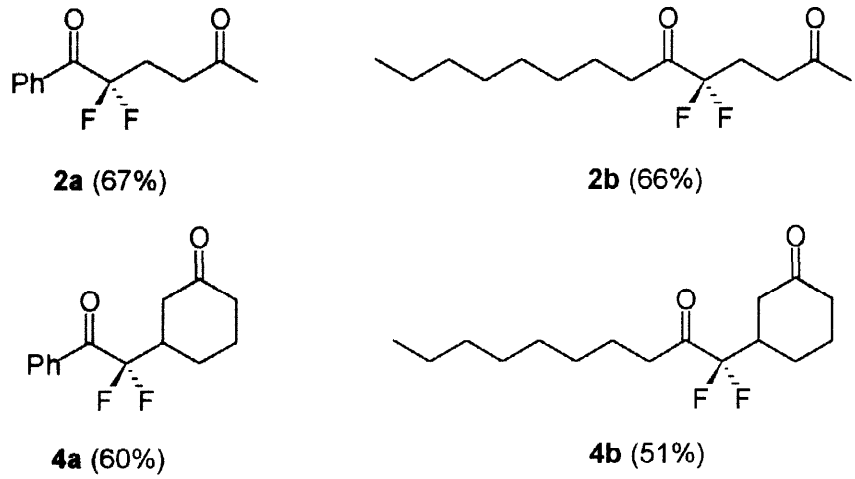
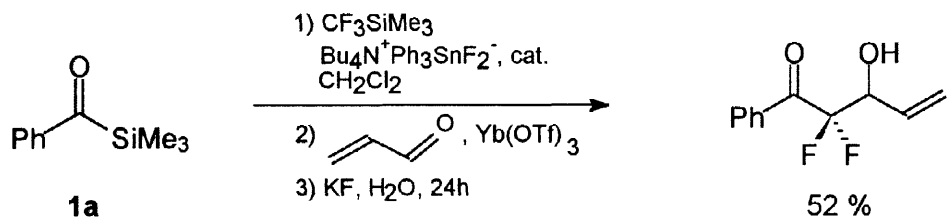


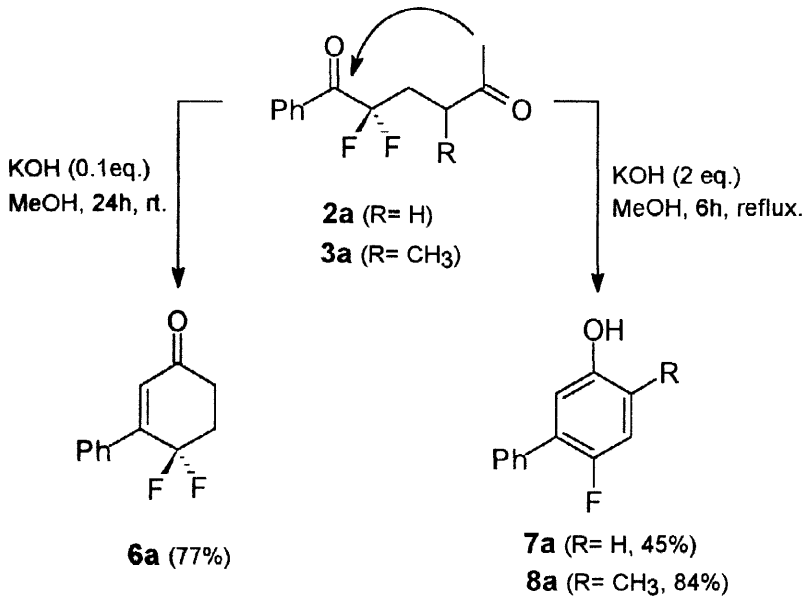
Chart 2



Scheme 3

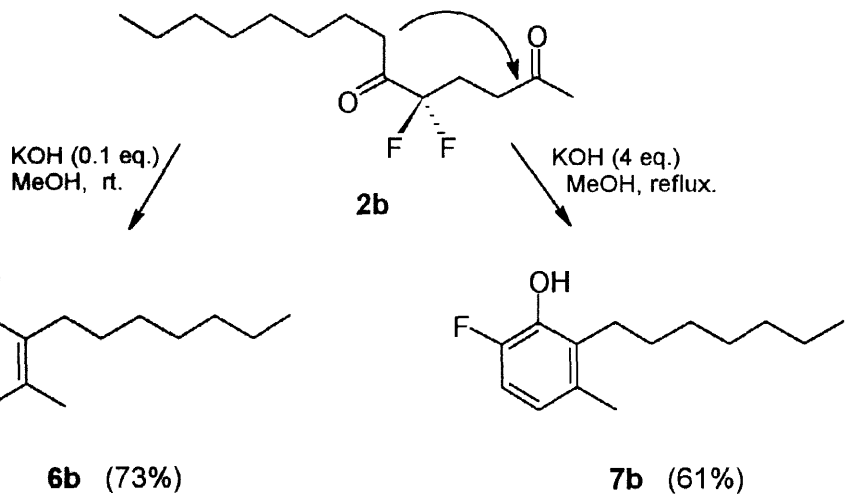
1,5-diketones are typical intermediates for annulation reactions. The 2,2-difluoro derivatives synthesized here present further interest: the fluorine atoms enhance the electrophilicity of the adjacent carbonyl group as well as the acidic character of the neighboring hydrogens. Hence the fluorine substitution is expected to control the regioselectivity of the cyclization. Furthermore, a possible HF elimination would lead to more conjugated systems. Thus we investigated the basic treatment of these diketones in order to find conditions which would lead selectively either to a *gem*-difluorocyclohexenone or to the corresponding fluorophenol. Following

preliminary experiments which showed that the selectivity strongly depends on the substitution pattern and on the stoichiometry of the base, we found that a catalytic amount of potassium hydroxide in THF allowed the mild and selective conversion of the diketone into an enone. Phenyl diketone **2a**, bearing a single enolizable site, led to 4,4-difluorocyclohexenone **6a**. As expected, when the diketone is treated with an excess of potassium hydroxide the reaction does not stop at the cyclohexenone stage. Such a treatment led directly to 4-fluoro-3-phenyl-phenol **7a**. Similarly diketone **3a** gave **8a** (Scheme 4).



Scheme 4

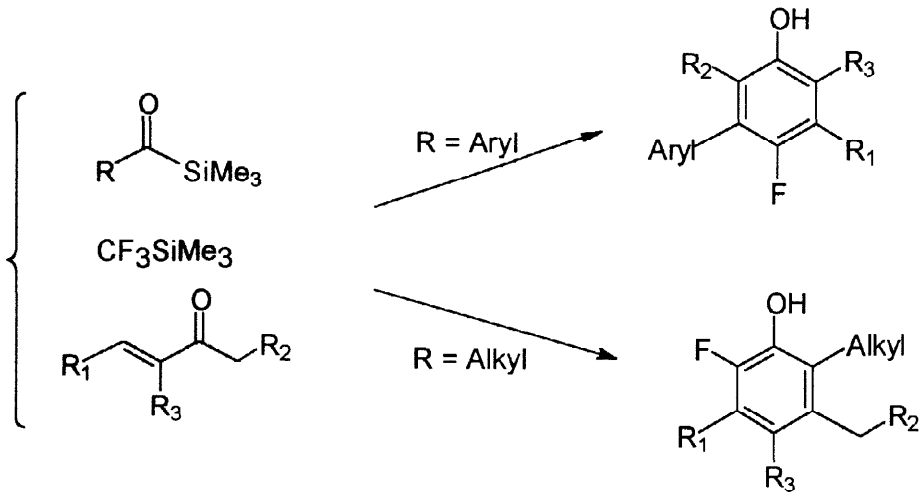
Interestingly, aliphatic diketone **2b**, which can cyclize through two possible enolates, reacted with complete regioselectivity the reaction being controlled by the activating effect of the difluoromethylene group, to give the 2,2-difluorocyclohexenone **6b**. As above, warming with an excess of base allowed the direct access to the corresponding ortho- fluorophenol **7b** (Scheme 5).



Scheme 5

Conclusion

These results extend the strategy of using TFMTMS, an acylsilane and the one-pot reaction of difluoroenoxysilane with an electrophile, here a conjugated enone. Although the process has been illustrated with only a limited number of reactants, we can conclude that it constitutes a convergent three component process which leads, with complete regioselectivity, to highly substituted ortho- or para-fluorophenols. The principle is depicted in Scheme 6.



Scheme 6

EXPERIMENTAL SECTION

General methods.

Melting points are uncorrected. FT-IR spectra were run on a MIDAS corporation apparatus. ^{1}H, ^{19}F, and ^{13}C NMR spectra were recorded on a BRUKER AC-250 spectrometer in $CDCl_3$ as the solvent. All chemical shifts are reported in parts per million against internal tetramethylsilane for ^{1}H and ^{13}C NMR spectra and $CFCl_3$ for ^{19}F NMR spectra. MS data were obtained on a Fison VG autospec 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 on a HP 5890 chromatograph equipped with a polydimethylsiloxane HP ultra I column and a flame ionization detector. Silicagel Merck 9385 (40-63 mm) was used for flash chromatography. Tetrabutylammonium difluorotriphenylstanate was prepared following the literature procedure.[13] The acylsilanes **1a** and **1b** were synthesized by the Brook and Corey method.[14] The puriss. quality of dichloromethane from Fluka was used for the Michael addition reactions.

Michael additions, general procedure.

In situ preparation of the difluoroenoxysilane. To a solution of acylsilane (1.5 mmol) and trifluoromethyltrimethylsilane (0.3 mL, 1.89 mmol)in CH_2Cl_2 (5 mL) under Argon was added a catalytic amount of tetrabutylammonium difluorotriphenylstanate (54 mg, 0.075 mmol). After 5 min stirring at 0°C, the reaction mixture was stirred for 25 min at room temperature. The formation of the difluoroenoxysilane was monitored by GC.

$TiCl_4$ catalysis. The reaction mixture was cooled down to -78°C and a solution of enone (2.25 mmol) in CH_2Cl_2 (5mL) and $TiCl_4$ (0.25 mL, 2.25 mmol) were added. After 35 min the reaction was quenched at -78°C by addition of a saturated Na_2CO_3 solution (10 mL). After extraction with CH_2Cl_2 (4x 20mL), the organic layer was washed with brine, dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by silicagel column chromatography

$BiCl_3$ / ZnI_2 catalysis. The enone (3 mmol), $BiCl_3$ (0.15 mmol) and freshly sublimated ZnI_2 (0.225 mmol) were added to the solution of difluoroenoxysilane at room temperature and the reaction mixture was stirred for 24h at room temperature. After hydrolysis with water the crude mixture was extracted with CH_2Cl_2 (4x 20mL), the organic layer was dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by silicagel column chromatography.

BF_3 .Et_2O/ menthol catalysis. The enone (3 mmol) and the menthol (1.65 mmol) were added to the solution of difluoroenoxysilane and the reaction mixture was cooled down to -78°C before addition of *BF_3 . Et_2O* (0.15 mL, 1.2 mmol). The mixture was stirred for 6h at room temperature and then quenched by addition of a saturated $NaHCO_3$ solution (10 mL). After extraction with CH_2Cl_2 (4x 20mL), the organic layer was washed with brine, dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by silicagel column chromatography.

$Yb(OTf)_3$ catalysis. The enone (3 mmol) and $Yb(OTf)_3$ (0.045 to 0.15 mmol) were added at room temperature to the solution of difluoroenoxysilane and the reaction mixture was stirred for 24h at room temperature. After hydrolysis with water the crude mixture was extracted with CH_2Cl_2 (4x 20mL), the organic layer was dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by silicagel column chromatography.

2,2-difluoro-1-phenylhexane-1,5-dione (2a). Colorless liquid (CH_2Cl_2/petroleum ether : 25/75). ^1H NMR 2.19 (s, 3H, H_6); 2.50 (tt, 2H, $^3J_{HF}$ = 18.4 Hz , $^3J_{HH}$ =7.4 Hz, H_3); 2.74 (t, 2H, $^3J_{HH}$ = 7.4 Hz, H_4); 7.48 (t, 2H, $^3J_{HH}$ = 7.7 Hz, H_{aro}); 7.63 (tm, 1H, $^3J_{HH}$ = 7.7 Hz, H_{aro}); 8.09 (d, 2H, $^3J_{HH}$ = 7.7 Hz, H_{aro}), ^{13}C NMR 28.0 (t, $^2J_{CF}$ = 23.6 Hz, C_3); 29.8 (C_6); 35.6 (C_4); 119.4 (t, J_{CF} = 253.0 Hz, C_2); 128.6 (C_{aro}); 130.1 (C_{aro}); 131.8 (C_{aro}); 134.3 (C_{aro}); 188.9 (t, $^2J_{CF}$ = 31.5 Hz, C_1); 205.6 (C_5), ^{19}F NMR -100.8 (t, $^3J_{HF}$ = 18.4 Hz, CF_2) ; IR 2957, 1723 (vs), 1703 (vs), 1360, 1269, 1179 cm^{-1}, MS m/e (%) 227 (M+1, 100), 209(77), 105(74); Anal. Calcd for $C_{12}H_{12}F_2O_2$ C, 63.71; H, 5.35. Found : C, 63.47; H, 5.50.

2,2-difluoro-4-methyl-1-phenylhexan-1,5-dione (3a). Colorless liquid (CH_2Cl_2/petroleum ether : 30/70). ^1H NMR 1.25 (d, 3H, $^3J_{HH}$=6.5 Hz , CH_3), 2.10 (m, 1H, H_3), 2.22 (s, 3H, H_6), 2.82 (m, 1H, H_3), 2.98 (ddq, 1H, $^3J_{HH}$ = 8 Hz, $^3J_{HH}$ = 6.5 Hz, $^3J_{HH}$ = 4 Hz, H_4), 7.49 (m, 2H, H_{aro}), 7.63 (m, 1H, H_{aro}), 8.09 (m, 2H, H_{aro}), ^{13}C NMR 17.9 (CH_3), 28.3 (C_6), 36.2 (t, $^2J_{CF}$= 22.6 Hz, C_3), 40.3 (C_4), 119.2 (t, J_{CF}= 253 Hz, C_2), 128.7 (C_{aro}), 130.1 (C_{aro}), 131.7 (C_{aro}), 134.3 (C_{aro}), 190.0 (t, $^2J_{CF}$= 30.5 Hz, C_1), 210.0 (C_5), ^{19}F NMR -99.5 (dt, 1F, J_{AB}= 288.3 Hz, $^3J_{HF}$= 18.8 Hz), -99.6 (dt, 1F, J_{AB}= 288.3 Hz, $^3J_{HF}$= 18.1 Hz); IR 2968 (s), 1709 (vs), 1601, 1450,1182 cm^{-1}, MS m/e (%) 241 (M+1, 100).

5,5-difluorotetradecane-2,6-dione (2b). Colorless liquid (CH_2Cl_2/petroleum ether : 45/55). ^1H NMR 0.88 (t, 3H, $^3J_{HH}$ = 6.7 Hz, H_{14}), 1.24-1.37 (m, 10H, CH_2), 1.61 (quint, 2H, $^3J_{HH}$=7.2 Hz, CH_2), 2.18 (s, 3H, H_1), 2.29 (tt, 2H, $^3J_{HF}$ =17.5 Hz, $^3J_{HH}$ =7.6 Hz, H_4), 2.64 (t, 2H, $^3J_{HH}$ = 7.6 Hz, H_7), 2.65 (tt, 2H, $^3J_{HH}$ = 7.2 Hz, $^4J_{HF}$=1.2 Hz, H_3), ^{13}C NMR 13.9, 22.6, 26.7 (t, $^2J_{CF}$ =23.6 Hz, C_4), 28.9- 29.2 (4C), 29.6, 31.7, 35.3, 36.1, 117.7 (t, $^1J_{CF}$ =252.0 Hz, C_5), 200.7 (t, $^2J_{CF}$ =30.5 Hz, C_6), 205.4 (C_2), ^{19}F NMR 108.0 (t, $^3J_{HF}$ =17.5 Hz, CF_2), IR 1169, 1213, 1725, 1744, 2930 cm^{-1}, MS m/e (%) 262 (M^+, 99), 244 (100), 141 (98)), Anal. Calcd for $C_{14}H_{24}F_2O_2$ C, 64.10; H, 9.22. Found : C, 64.39; H, 9.48.

3-(1,1-difluoro-2-oxo-2-phenylethyl)cyclohexanone (4a). Colorless liquid (CH_2Cl_2/petroleum ether : 50/50). ^1H NMR 1.60-2.65 (m, 9H), 7.50 (tm, $^3J_{HH}$=8.0 Hz, 2H), 7.65 (t, $^3J_{HH}$=8.0 Hz, 1H), 8.09 (dd, $^3J_{HH}$=8.0 Hz, $^4J_{HH}$=1.15, 2H), ^{13}C NMR 23.2, 24.12, 39.8, 42.0 (t, $^2J_{HF}$ =22.6 Hz, CH), 50.2, 118.8 (t, J_{CF} =256.9 Hz, C_2), 128.8, 130.0, 132.3, 134.4, 188.9 (t, $^2J_{CF}$ = 29.5, C_1), 208.5, ^{19}F NMR :-107.1 (dd, 1F, $^3J_{HF}$ =14.0 Hz, J_{AB} = 282.5 Hz), -108.9 (dd, 1F, $^3J_{HF}$ = 15.2 Hz, J_{AB} = 282.5 Hz), IR 1125, 1688, 2872, 2951 cm^{-1}, MS m/e (%) 253 (M+1, 22), 232 (48), 105 (100).

3-(1,1-difluoro-2-oxodecanyl)cyclohexanone (4b). Colorless liquid (CH_2Cl_2/petroleum ether : 50/50). ^1H NMR 0.86 (t, 3H, $^3J_{HH}$ =6,7 Hz, CH_3), 1.14-1.38 (m, 10H, CH_2), 1.50-1.65 (m, 4H, CH_2), 1.85-2.05 (m, 2H, CH_2), 2.05-2.50 (m, 4H, CH_2), 2.62 (tt, 2H, $^3J_{HH}$ =7.2 Hz, $^4J_{HF}$ =1.1 Hz, $H_{3\ side\ chain}$), ^{13}C NMR 13.9, 22.5, 23.4, 24.1, 28.9- 29.2(4C), 31.7, 37.1, 39.5, 40.7 (t, $^2J_{CF}$ =22.6 Hz, C_3), 40.8, 117.3 (t, J_{CF} =255.9 Hz, CF_2), 200.9 (t, $^2J_{CF}$ =30.5 Hz, $C_{2'}$), 208.1 (C_1), ^{19}F NMR -113.7 (dd, 1F, J_{AB} =274.6 Hz, $^3J_{HF}$ =11.4 Hz, CF_2), -115.5 (dd, 1F, J_{AB} =274.6 Hz, $^3J_{HF}$ =15.3 Hz, CF_2) ; IR 2930 (vs), 2859, 1742, 1721 (vs) cm^{-1}, MS m/e (%) 288 (M^+, 23), 268 (38), 141 (100), Anal. Calcd for $C_{16}H_{26}F_2O_2$ C, 66.65; H, 9.09. Found, C, 66.36; H, 9.23.

Annulation reactions, general procedure.

To a solution of 1,5-diketone (0.3-0.5 mmol) in methanol (2-5 mL) was added a catalytic amount of crushed KOH (0.1 eq.). The mixture was vigorously stirred at room temperature until total transformation of the starting material. The reactions were monitored by TLC. The crude mixture was treated with a saturated

NH_4Cl solution and extracted with CH_2Cl_2 (3x20 mL). The combined organic layer was dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by silicagel column chromatography.

4,4-difluoro-3-phenylcyclohex-2-en-1-one (6a). White solid, (CH_2Cl_2/petroleum ether : 30/70). mp= 62-63 C, ^1H NMR 2.60 (tt, 2H, $^3J_{HF}$=13.5 Hz, $^3J_{HH}$=6.5 Hz, H_5), 2.76 (t, 2H, $^3J_{HH}$=6.5 Hz, H_6), 6.34 (t, 1H, $^4J_{HF}$ =1.5 Hz, H_2), 7.39-7.45 (m, 3H, H_{aro}), 7.56-7.60 (m, 2H, H_{aro}), ^{13}C NMR 32.9 (t, $^2J_{CF}$=25.6 Hz, C_5), 33.9 (t, $^3J_{CF}$ = 4.5 Hz, C_6), 118.5 (t, J_{CF} = 240.2 Hz, C_4), 127.8, 128.6, 130.2, 130.4, 132.4, 151.6 (t, $^2J_{CF}$= 25.6 Hz, C_3), 196.0 (C_1), ^{19}F NMR -94.7 (t, $^3J_{HF}$=13.5 Hz, CF_2), IR 1678 (vs), 1615, 1111, 468 (vs) cm^{-1}, MS m/e (%) 208 (M^+, 100), 180 (68).

6,6-difluoro-2-heptyl-3-methylcyclohex-2-en-1-one (6b). Colorless liquid (CH_2Cl_2/ petroleum ether : 30/70). ^1H NMR 0.88 (t, 3H, $^3J_{HH}$=6.5 Hz, CH_3), 1.23-1.40 (m, 10H, 5 CH_2), 2.00 (s, 3H, CH_3), 2.36 (tt, 2H, $^3J_{HF}$ =15.2 Hz, $^3J_{HH}$=6.1 Hz, H_5), 2.33 (t, 2H, $^3J_{HH}$=6.1 Hz, CH_2), 2.56 (t, 2H, $^3J_{HH}$=6.1 Hz, H_4), ^{13}C NMR 21.2, 22.6, 25.6, 28.6, 29.1, 29.3 (2C), 29.5, 31.2 (t, $^2J_{CF}$=22.6 Hz, C_5), 31.8, 112.9 (t, J_{CF}=246.1 Hz, C_6), 134.7, 156.6, 185.3 (t,$^2J_{CF}$=24.6 Hz, C_1), ^{19}F NMR -111.0 (t, $^3J_{HF}$=15.2 H, 2F, CF_2), IR 2928 (vs), 2856, 1694 (s), 1624, 1202, 1088 cm^{-1}, MS m/e (%) 244 (M^+, 8), 229 (40), 124 (100).

Fluorophenols (5) preparation.

To a solution of 1,5-diketone (0.3-0.5 mmol) in methanol (2-5 mL) was added an excess of crushed KOH (2-4 eq.). The mixture was vigorously stirred at reflux until total transformation of the starting material. The reactions were monitored by TLC. A work-up following the same procedure as for the annulation reactions gave pure fluorophenols after silicagel column chromatography.

4-fluoro-3-phenylphenol (7a). Colorless liquid (CH_2Cl_2/petroleum ether : 30/70). ^1H NMR 5.42 (s, 1H, O*H*), 6.77 (dt, 1H, $^3J_{HH}$=8.7 Hz, $^4J_{HH}$= $^4J_{HF}$=3.4 Hz, H_6), 6.91 (dd, $^4J_{HF}$=6.1 Hz, $^4J_{HH}$=3.4 Hz, H_2), 7.03 (dd, $^3J_{HH}$ =8.7 Hz, $^3J_{HF}$=9.9 Hz, H_5), 7.33-7.58 (m, 5H_{aro}), ^{13}C NMR 115.2 (d, $^2J_{CF}$=7.9 Hz, C_5), 116.6, 116.9 (d, $^3J_{CF}$ =3.9 Hz), 127.8, 128.4, 128.8, 129.8 (d, $^2J_{CF}$=15.6 Hz, C_3), 135.5, 151.5 (C_1), 154.2 (d, J_{CF}=240.2 Hz, C_4), ^{19}F NMR -129.3 (m, 1F), IR 3522 (b), 1479, 1431, 1265 (s), 740 (vs), 702 cm^{-1}; MS m/e (%) 188 (M^+,100), 159 (90), 133 (85).

6-fluoro-3-methyl-2-heptylphenol (7b). Colorless liquid (CH_2Cl_2/petroleum ether : 30/70). ^1H NMR 0.91 (t, 3H, $^3J_{HH}$=6.9 Hz, CH_3), 1.26-1.55 (m, 1OH, 5 CH_2), 2.26 (s, 3H, CH_3), 2.66 (t, 2H, $^3J_{HH}$=7.6 Hz, CH_2), 5.05 (d, 1H, $^4J_{HF}$=3.4 Hz, O*H*), 6.64 (dd, $^3J_{HH}$=8.4 Hz, $^4J_{HF}$=5.7 Hz, 1H, H_4), 6.82 (dd, $^3J_{HH}$=8.4 Hz, $^3J_{HF}$=9.9 Hz, 1H, H_5) ; ^{13}C NMR 14.1, 19.0, 22.7, 26.6, 29.0, 29.2, 29.9, 31.9, 111.7 (d, $^2J_{CF}$=17.7 Hz, C_5), 121.1 (d,

$^3J_{CF}$=5.9 Hz, C_4), 129.9, 132.6, 141.3 (d, $^2J_{CF}$=11.8 Hz, C_1), 149.5 (d, J_{CF}=243.3 Hz, C_6) ^{19}F NMR -145.0 (m), IR 3592, 2957 (vs), 2857, 1493 (s), 1468, 1263, 1229, 793 cm^{-1}.

4-fluoro-2-methyl-5-phenylphenol (8a). Colorless liquid (CH_2Cl_2/petroleum ether : 50/50). ^{1}H NMR 2.28 (s, 3H, CH_3), 4.79 (s, 1H, O*H*), 6.85 (d, 1H, $^4J_{HF}$= 6.7 Hz, H_6), 6.93 (d, 1H, $^3J_{HF}$= 11 Hz, H_3), 7.34-7.55 (m, 5H, H_{aro}) ; ^{13}C NMR 15.6 (CH_3), 116.2, 117.9, 118.2, 124.7 (d, $^2J_{CF}$= 6.9 Hz), 126.9 (d, $^2J_{CF}$= 10.7 Hz), 127.5, 128.4, 128.8, 135.7, 153.8 (d, J_{CF}= 242.5 Hz, C_4) ; ^{19}F NMR -129.7 (dd, $^3J_{HF}$=10.9 Hz, $^4J_{HF}$=6.7 Hz) ; IR 3283 (b), 1177 (s), 762, 696 cm^{-1} ; MS m/e (%) 202 (M^+,100), Anal. Calcd for $C_{13}H_{11}FO$: C, 77.21; H, 5.48. Found, C, 76.97; H, 5.21.

Acknowledgements.

The authors thank the "Ministère de l'Education Nationale, de l'Enseignement Supérieur et de la Recherche" for a fellowship (OL) and Henri Baillia and Sylvie Lanthony for their help in NMR and Elemental Analysis.

REFERENCES AND NOTES

1 Yamana, M. ; Ishihara, T. ; Ando, T. *Tetrahedron Lett.* **1983**, *24*, 507-510.

2 Jin, F. ; Jiang, B. ; Xu, Y. *Tetrahedron Lett.* **1992**, *33*, 1221-1224.

3 Brigaud, T. ; Doussot, P. ; Portella, C. *J. Chem. Soc., Chem. Commun.* **1994**, 2117-2118.

4 Prakash, G. K. S. ; Yudin, A. *Chemical Reviews* **1997**, *97*, 757-786.

5 Brigaud, T. ; Lefebvre, O. ; Plantier-Royon, R. ; Portella, C. *Tetrahedron Lett.* **1996**, *37*, 6115-6116.

6 Narasaka, N. ; Soai, R. ; Mukaiyama, T. *Chem. Lett.* **1974**, 1223-1224. Narasaka, N. ; Soai, R. ; Aiwacha, Y. ; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 779-783.

7 Le Roux, C. ; Gaspard-Iloughmane, H. ; Dubac, J. ; Jaud, J. ; Vignaux, P. *J. Org. Chem.* **1993**, *58*, 1835-1839.

8 Duhamel, P. ; Dujardin, G. ; Hennequin, L. ; Poirier, J.-M. *J. Chem. Soc., Perkin Trans. 1* **1992**, 387-396.

9 a) Aldol reaction : Kobayashi, S. *Chem. Lett.* **1991**, 2187-2090; Kobayashi, S. ; Hachiya, I. *Tetrahedron Lett.* **1992**, *33*,1625-1628. b) Michael and Diels Alder reactions : Kobayashi, S. ; Hachiya, I. ; Takahori, T. ; Araki, M. ; Ishitani, H. *Tetrahedron Lett.* **1992**, *33*, 6815-6818. c) Friedel-Crafts reactions : Kawada, A. ; Mitamura, S. ; Kobayashi, S. *J. Chem. Soc., Chem. Commun.* **1993**, 1157-1158.

10 Application of this strategy to aldol reactions and the synthesis of α,α-difluoro-β-ketols will be reported in a forthcoming paper.

11 Kodama, Y. ; Yamane, H. ; Okumura, M. ; Shiro, M. ; Taguchi, T. *Tetrahedron* **1995**, *51*, 12217-12228.

12 Kuroboshi, M. ; Ishihara, T. *Tetrahedron Lett.* **1987**, *28*,6481-6484.

13 Gingras, M. *Tetrahedron Lett.* **1991**, *32*, 7381-7384.

14 Brook, A.G. ; Duff, J.M. ; Davis, N.R. *J. Am. Chem. Soc.* **1967**, *89*, 431-434 ; Corey, E.J. ; Seebach, D. ; Freedman, R. *J. Am. Chem. Soc.* **1967**, *89*, 434-436.