α-Trifluoromethyl-Destabilized Cations. A Route to 1-(Trifluoromethyl)tetralins by Trifluoroacetolysis of 5-Aryl-1,1,1-trifluoropentan-2-ols and Derivatives

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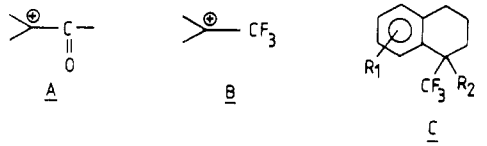
Trifluoroacetolysis of 5-aryl-1,1,1-trifluoropentan-2-ols 1 and their 2-aryl (2) and 2-methyl (3) analogues has been studied in search of a route to 1-(trifluoromethyl)tetralins. The results reflect the relative stabilities of the incipient carbocation intermediates. Thus the cyclization of 1 triflate depends on the para substituent on the aryl group and is interpreted in terms of Ar_2-6 assistance. Cyclizations of 2 are quite general and give 1-(trifluoromethyl)tetralins in high yields, reflecting a high degree of carbocationic character in the intermediates prior to cyclization. Attempted cyclization of 3 triflate gave only olefins and the parent alcohol.

Introduction

Solvolytic studies have shown that increasing demand on an incipient carbocation can enhance intramolecular assistance (k_Δ).[1] A number of recent studies have been devoted to destabilized carbocations substituted by an electron-withdrawing group.[2] Thus carbocationic cyclizations involving k_Δ might be favored when they are initiated by an incipient destabilized carbocation; this approach has been successful, for example, with α-acylcarbenium A.[3]



A B C

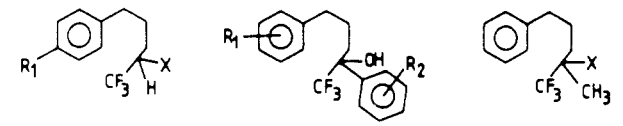
We here describe our attempts to apply the same approach with highly destabilized α-trifluoromethyl carbocations B;[4,5] we have studied the trifluoroacetolysis of 5-aryl-1,1,1-trifluoropentan-2-ols 1 and their 2-aryl (2) and 2-methyl (3) analogues in search of a route to 1-(trifluoromethyl)tetralins C. This approach could provide an easy way of introduction of the trifluoromethyl group into an aliphatic cycle, which is still an actual problem.[6]

Results

The course of the trifluoroacetolysis of 1, 2, and 3 prepared from ketones 4[7] is strongly dependent on the structure of the starting material.

Trifluoroacetolysis of 1. Cyclizations were attempted by heating 1 in the presence of trifluoroacetic acid/trifluoroacetic anhydride (Table I). From the alcohol **1a** only the trifluoroacetate **1g** was obtained, and no reaction occurred with tosylate **1b**. Triflates **1c** (R_1 = H) and **1d** (R_1 = CH_3) cyclized to tetralins **5c** and **5d** in yields of 93% and 51%, respectively, requiring long reactions at high temperatures. On the other hand, **1e** (R_1 = OCH_3) and **1f** (R_1 = Cl) did not cyclize. No effect on the results was noted on adding 1 equiv of CF_3CO_2Na or a small amount of H_2SO_4, or by attempting the cyclization in hexafluoroisopropyl alcohol.

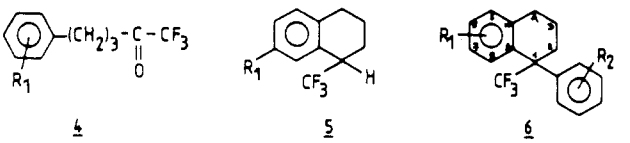
Trifluoroacetolysis of 2. Heating **2a–h** in trifluoroacetic acid containing 2×10^{-2} M H_2SO_4 at reflux temperature gave 1-aryl-1-(trifluoromethyl)tetralins 6 in excellent yields (Table II).



1 2 3

	1: R_1	1: X	2: R_1	2: R_2
a	H	OH	H	H
b	H	OTs	p-CH_3	H
c	H	OTf	p-OCH_3	H
d	CH_3	OTf	p-Cl	H
e	OCH_3	OTf	m-Cl	H
f	Cl	OTf	H	p-OCH_3
g	H	O_2CCF_3	H	p-Cl
h	CH_3	OH	H	m-Cl
i	OCH_3	OH		
j	Cl	OH		

3: a, X = OH; b, X = OMs; c, X = OTf; d, X = O_2CCF_3; e, X = $OCH(CF_3)_2$



4 5 6

4: a, R_1 = H; b, R_1 = p-CH_3; c, R_1 = p-OCH_3; d, R_1 = p-Cl; e, R_1 = m-Cl

5: c, R_1 = H; d, R_1 = CH_3

6	R_1	R_2
a	H	H
b	7-CH_3	H
c	7-OCH_3	H
d	7-Cl	H
e	6-Cl	H
f	H	p-OCH_3
g	H	p-Cl
h	H	m-Cl

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Table I. Trifluoroacetolysis[a] of 5-Aryl-1,1,1-trifluoropentan-2-ol 1a and Derivatives

starting material	rctn condtns		products (isolated yield)		run
	time, h	temp, °C	tetralin	other products	
1a	48	140	–	**1g** (75%)	1
1b	48	140	–	starting material	2
1c	48	140	**5c** (93%)	–	3
1d	16	160[b]	**5d** (51%)	tars	4
1e	48	110[c]	–	starting material	5
1f	48	160[b]	–	starting material	6

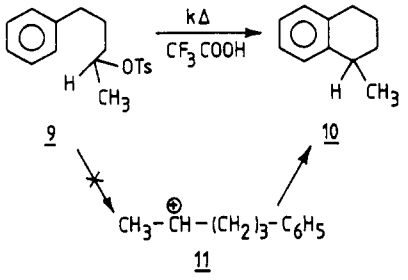
[a] Addition of CF_3CO_2Na (1 mol) or a few drops of H_2SO_4 (95%) did not change the course of the reaction. [b] No reaction occurred at 140 °C. [c] At 120 °C, depending on the reaction time, starting material or (and) tars were obtained.

Table II. Trifluoroacetolysis of 2,5-Diphenyl-1,1,1-trifluoropentan-2-ol and Related Compounds 2

starting material	rctn condtns[a]		tetralin (isolated yields)	run
	time	temp		
2a	15 h	120 °C[b]	**6a** (87%)	7
2a	0.5 h	reflux	**6a** (85%)	8
2b	0.5 h	reflux	**6b** (85%)	9
2c	0.5 h	reflux	**6c** (95%)	10
2d	1 h	reflux	**6d** (90%)	11
2e	0.5 h	reflux	**6e** (90%)	12
2f	5 min	reflux	**6f** (95%)	13
2g	1 h	reflux	**6g** (85%)	14
2h	6 h	reflux	**6h** (95%)	15

[a] A 2×10^{-2} M solution of H_2SO_4 in CF_3COOH was used (25 mL for 1.5 mmol of **2**). [b] Pure CF_3COOH was used.

Scheme I



Trifluoroacetolysis of 3. No tetralins could be obtained by trifluoroacetolysis of **3** under a variety of conditions (Table III).

Discussion

Cyclization of compounds **1** requires an excellent leaving group (triflate) and severe reaction conditions. Even so, cyclization occurred only when the para substituent R_1 on the aromatic ring was H or CH_3 and failed when it was OCH_3 or Cl, which are known to be deactivating groups in the meta position.[8] On the other hand, cyclizations of **2** occurred under relatively mild conditions in high yields, regardless of the leaving group or the substituents on the aromatic rings. These differences suggest that reactions of **1** and **2** occur by two different pathways.

It seems reasonable that cyclizations of **1** occur by a concerted k_Δ process that involves nucleophilic assistance of the δ phenyl group.

Such a participation in the synthesis of tetralins has been reported;[9,10] solvolysis of 5-phenylpentane tosylate **9** in trifluoroacetic acid gives 1-methyltetralin (**10**) by phenyl assistance and not via the carbocation **11**[10b] (Scheme I).

The formation of the trifluoromethyl carbocation analogue **12** (Scheme II) is ruled out in the cyclizations of **1c** and **1d** since **12** is 60 kcal/mol less stable than **11**.[2b,c,11] Furthermore, the fact that the product of these cyclizations is **5** and not the isomer **5′**[17] (Scheme II) suggests that the

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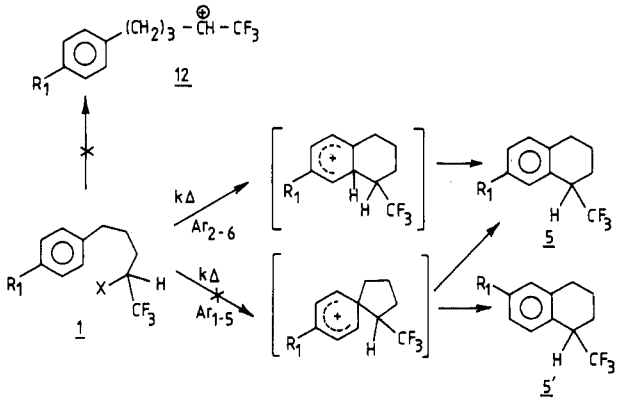
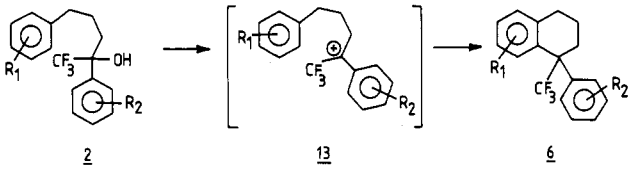


Scheme III



Scheme IV

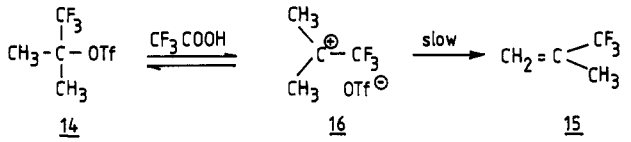


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Table III. Trifluoroacetolysis of 2-Methyl-5-phenyl-1,1,1-trifluoropentan-2-ol and Derivatives 3

starting material	rctn condtns: solvent	buffer	time, h	temp, °C	products (isolated yields)	run
3a	CF_3COOH	–	15	140	**3d** (97%)	16
3a	$CF_3COOH + H_2SO_4$[a]	–	15	80	**3d** (80%)	17
3b	CF_3COOH	CF_3CO_2Na	20	140	(**7** + **8**) (20%) + tars[b]	18
3c	CF_3COOH	CF_3CO_2Na	3	80	**8** (8%) + **7** (25%) + **3a**[c] (20%) + P[d] (45%)	19
3c	HFIP	CF_3CO_2Na	16	100	**8** (11%) + **7** (28%) + **3a**[c] (21%) + P[d] (38%)	20
3c	HFIP	Na_2CO_3	16	100	**8** (14%) + **7** (24%) + **3a**[c] (20%) + P[d] (40%)	21
3c	HFIP		16	100	**8** (20%) + **3e** (80%)	22

[a] A 2×10^{-2} M solution of H_2SO_4 in CF_3COOH (25 mL for 1.5 mmol of **3**). [b] At 120 °C, no reaction occurred. [c] **3a** is formed by a solvolytic process since **3c** is stable under workup conditions. [d] Polymeric material.

Table IV. Influence of R_1 and R_2 on the Cyclization Rates of Compounds 2[a]

R_1	R_2	$\tau_{0.5}$[b]
H	H	15 min
p-OMe	H	15 min
p-Cl	H	20 min
m-Cl	H	15 min
H	*p*-OMe	1 min
H	*p*-Cl	25 min
H	*m*-Cl	2 h 45 min

[a] In a 2×10^{-2} M solution of H_2SO_4 in CF_3COOH at reflux (25 mL for 1.5 mmol of **2**). [b] Time necessary for the disappearance of half of starting material.

pathway for δ-phenyl participation is Ar_2-6 and not Ar_1-5 because the latter should lead in part to **5′**.[10c] The failure of **1e** and **1f** to cyclize supports this presumption.

The formation of tetralins **6** from **2** can be interpreted as involving ionization of the C–O^+H_2 bond, leading to high development of a positive charge in the transient intermediate **13** (Scheme III). This assumption is supported by the fact that formation of α-aryl-α-trifluoromethyl carbocations is rate-determining in the trifluoroacetolysis of α-aryl-α-trifluoromethyl sulfonates.[12] Additional support is found in our rate experiments on cyclization of **2** (Table IV). In cyclizations of **2** (R_2 = H), $\tau_{0.5}$ for disappearance of starting material was about 15 min, regardless of the substituent R_1. In contrast, when R_1 = H, the nature of R_2 has a strong influence on $\tau_{0.5}$. The latter effect can be correlated with the σ^+ values for the R_2 groups, which reflect the relative stabilities of the carbocations **13**: the more stable the carbocation (R_2 = OCH_3, σ^+ = –0.78), the faster the reaction ($\tau_{0.5}$ = 1 min), whereas when R_2 = *m*-Cl (σ^+ = +0.40), $\tau_{0.5}$ = 2.75 h.

Although no cyclizations occurred with **3**, it is interesting that triflate **3c** is partially converted into alcohol **3a**. This result is surprising in view of the solvolysis, under the same conditions, of the analogous triflate **14** to the elimination product **15** (Scheme IV).[13] Our results, without kinetic data, do not allow any conclusion about the mechanism of formation of olefins **7** and **8** from **3c**.

Experimental Section

Infrared spectra were taken on a 1420 Perkin-Elmer infrared spectrophotometer. NMR spectra were recorded on either a Varian EM-360A (^1H and ^{19}F) or a CFT20 (^{13}C) spectrometer, with $CDCl_3$ as solvent and Me_4Si (^1H and ^{13}C) or $CFCl_3$ (^{19}F) as internal standard. In ^{13}C NMR data, reported signal multiplicities are related to C–F coupling. The trifluoromethyl group and related J_{CF} coupling constants are of great help in ^{13}C spectra assignments,[17] since they supplement the information given by the simple routine techniques[14] of off resonance and additivity rules.[15] Mass spectra were obtained in a NERMAG R10-10 apparatus coupled to a gas-phase chromatograph (capillary column CPSIL-5, 25 m) and in a KRATOS MS 50 spectrometer.

5-Aryl-1,1,1-trifluoropentan-2-ones 4. A solution of ethylmagnesium bromide (0.2 mol) in anhydrous ether (100 mL) was added dropwise under nitrogen to a stirred solution of trifluoroacetic acid (0.2 mol) in anhydrous ether (100 mL) at –5 °C. The reaction mixture was allowed to warm to room temperature and produced the magnesium bromide salt of trifluoroacetic acid. A solution of the appropriate 3-aryl-1-bromopropane (0.15 mol) in anhydrous ether (150 mL) was added, dropwise with stirring, to magnesium (0.15 mol) in anhydrous ether (10 mL) at a rate adjusted to maintain a steady reflux. After 2 h, to the resulting Grignard solution was added dropwise, under nitrogen, the trifluoroacetic salt suspension at –5 °C. After being stirred for 1 h at room temperature and refluxed for 1 h, the mixture was cooled and hydrolyzed by 100 mL of HCl (10%) added dropwise at 0 °C. The aqueous layer was extracted with ether. The combined organic layers were washed with brine, dried ($MgSO_4$), concentrated, and distilled. The preparation of the 3-aryl-1-bromopropanes which are not commercially available is described below.

5-Phenyl-1,1,1-trifluoropentan-2-one (4a): yield 48%; bp 90 °C (10 mmHg); IR ($CHCl_3$) 1760 ($\nu_{C=O}$), 1160, 1140 cm^{-1}; MS, *m/e* 216 (M^+), 147 ($M^+ - CF_3$), 136, 118, 104, 91; ^1H NMR δ 2.0 (m, 3, CH_3), 2.7 (m, 4, $(CH_2)_2$), 7.2 (m, 5, Ar H); ^{19}F NMR δ –80; ^{13}C NMR δ 24.0, 34.6, 35.5 (3 × CH_2), 126.4, 128.5, 128.7 (Ar CH), 141.0 (quatern arom C), 116.0, (q, *J* = 292 Hz, CF_3), 191.0 (q, *J* = 35 Hz, C=O); high-resolution mass spectrum M^+ 216.0763, calcd for $C_{11}H_{11}OF_3$ 216.0762.

5-(*p*-Methylphenyl)-1,1,1-trifluoropentan-2-one (4b): purified by chromatography (SiO_2, pentane/Et_2O, 10%); yield 45%; ^1H NMR δ 1.8 (t, *J* = 7 Hz, 2, CH_2), 2.1 (s, 3, CH_3), 2.5 (m, 4, $(CH_2)_2$), 7 (s, 4, Ar H); ^{19}F NMR δ –80; ^{13}C NMR δ 21.0 (CH_3), 24.2, 34.2, 35.6 (3 × CH_2), 116.0 (q, *J* = 292 Hz, CF_3), 128.5, 129.4 (Ar CH), 136.0, 138.0 (quatern arom C), 191.0 (q, *J* = 35 Hz, C=O).

5-(*p*-Methoxyphenyl)-1,1,1-trifluoropentan-2-one (4c): purified by chromatography (SiO_2, pentane/Et_2O, 10%); yield 46%; bp 82 °C (0.5 mmHg); ^1H NMR δ 1.9 (m, 2, CH_2), 2.6 (m, 4, $(CH_2)_2$), 3.7 (s, 3, OMe), 6.9 (q, *J* = 9 Hz, 4, Ar H); ^{19}F NMR δ –80; ^{13}C NMR δ 24.2, 33.7, 35.6 (3 × CH_2), 55.2 (OCH_3), 122.0 (q, *J* = 286 Hz, CF_3), 114.0, 129.5 (Ar CH), 133.0, 158.0 (quatern arom C), 192.0 (q, *J* = 34 Hz, C=O); high-resolution mass spectrum M^+ 246.0868, calcd for $C_{12}H_{13}O_2F_3$ 246.0867.

5-(*p*-Chlorophenyl)-1,1,1-trifluoropentan-2-one (4d). The crude product was distilled (bp 86 °C (0.3 mmHg)) and the pure ketone was obtained in 46% yield: ^1H NMR δ 2.0 (m, 2, CH_2), 2.6 (m, 4, $(CH_2)_2$), 7.1 (m, 4, Ar H); ^{19}F NMR δ –80; ^{13}C NMR δ 24.0, 34.1, 35.6 (3 × CH_2), 116.0 (q, *J* = 292 Hz, CF_3), 129.0, 130.0 (Ar CH), 132.3, 139.6 (quatern arom C), 191.4 (q, *J* = 35 Hz, C=O); high-resolution mass spectrum M^+ 250.0374, calcd for $C_{11}H_{10}OF_3Cl$ 250.0372.

5-(*m*-Chlorophenyl)-1,1,1-trifluoropentan-2-one (4e). Distillation of the crude product (bp 72 °C (0.2 mmHg)) afforded the pure ketone in 43% yield: ^1H NMR δ 1.8 (m, 2, CH_2), 2.4 (m, 4, $(CH_2)_2$), 6.4 (m, 4, Ar H); ^{19}F NMR δ –80; ^{13}C NMR δ 24.0, 34.5, 35.7 (3 × CH_2), 116.0 (q, *J* = 292 Hz, CF_3), 126.8, 127.0, 128.8, 130.2 (Ar CH), 134.6, 143.3 (quatern arom C), 191.0 (q, *J* = 35

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Hz, C=O); high-resolution mass spectrum M^+ 250.0374, calcd for $C_{11}H_{10}OF_3Cl$ 250.0372.

Preparation of 3-(*m*/*p*-chlorophenyl)propanol[16] and 1-bromo-3-(*m*/*p*-chlorophenyl)propane was undertaken prior to the preparation of ketones **4d** and **4e**.

3-(*m*-Chlorophenyl)propanol: bp 115 °C (0.4 mmHg); yield 63%.

3-(*p*-Chlorophenyl)propanol: bp 98 °C (0.1 mmHg); yield 56%.

1-Bromo-3-(*m*-chlorophenyl)propane: bp 75 °C (0.1 mmHg); yield 77%.

1-Bromo-3-(*p*-chlorophenyl)propane: bp 92 °C (0.3 mmHg); yield 65%.

Alcohols 1a, 1h, 1i, 1j, and Derivatives. For alcohols **1a**, **1h**, **1i**, and **1j**, a solution of the corresponding ketone **4** (10 mmol) in anhydrous ether (20 mL) was added to a stirred suspension of $LiAlH_4$ (10 mmol) in anhydrous ether (20 mL). After 2 h at room temperature, the reaction mixture was hydrolyzed in ether and water. The organic layer was extracted, washed, and dried over magnesium sulfate. After evaporation of the solvent and distillation, the pure alcohol was obtained.

5-Phenyl-1,1,1-trifluoropentan-2-ol (1a). Starting ketone **4a** was reduced in **1a** (80%): bp 72 °C (0.1 mmHg); IR (film) 3350 (ν_{OH}), 2950, 1180, 1140 cm^{-1}; ^1H NMR δ 1.7 (m, 4, $(CH_2)_2$), 2.2 (s, 1, OH), 2.7 (m, 2, CH_2), 3.9 (m, 1, $CHCF_3$), 7.2 (s, 5, Ar H); ^{19}F NMR δ −80 (d, J = 6.6 Hz); ^{13}C NMR (Table V, supplementary material).

5-Phenyl-1,1,1-trifluoropentan-2-ol Tosylate (1b). Tosyl chloride (6.5 mmol) was added to a stirred solution of alcohol **1a** (4.5 mmol) in pyridine (20 mL) with 10 mg of 4-(dimethylamino)pyridine (DMAP). The solution was allowed to stand overnight at room temperature, extracted with CH_2Cl_2, and washed until there was no pyridine left. After evaporation of the solvent, the crude tosylate was used without any further purification (yield 90%): ^1H NMR δ 1.8 (m, 4, $(CH_2)_2$), 2.2 (s, 3, CH_3), 2.5 (m, 2, CH_2), 4.8 (m, 1, aliph CH), 7.2 (m, 9, Ar H).

5-Phenyl-1,1,1-trifluoropentan-2-ol Triflate (1c). At 0 °C, under argon, to a stirred mixture of pyridine (4 mL) and CH_2Cl_2 (15 mL), both filtered on alumina, were slowly added, via a syringe, successively triflic anhydride (3 mmol) and alcohol **1a** (2 mmol). The reaction mixture was stirred for 4 h at 0 °C, poured on acidified (HCl, 15%) water and ice, then extracted in CH_2Cl_2, washed until neutral, and dried ($MgSO_4$). After removal of the solvent, **1c** was obtained in 95% yield: bp 92 °C (12 mmHg); IR (film) 1440, 1180, 1140 cm^{-1}; ^1H NMR δ 1.9 (m, 4, $(CH_2)_2$), 2.7 (m, 2, CH_2), 5.05 (m, 1, aliph CH), 7.15 (s, 5, Ar H); ^{19}F NMR δ −74, −77; ^{13}C NMR δ 26.0, 28.5, 35.2 (3 × CH_2), 82.2 (q, J = 34.2 Hz, CCF_3), 122.7 (q, J = 280 Hz, CF_3), 126.8, 128.7, 129 (Ar CH), 140.8 (quatern arom C).

5-(*p*-Methylphenyl)-1,1,1-trifluoropentan-2-ol Triflate (1d). The alcohol **1h** (for preparation of **1h** see below) was converted to the triflate **1d** by treatment with pyridine and triflic anhydride in 73% yield: ^1H NMR δ 1.7 (m, 4, $(CH_2)_2$), 2.3 (s, 3, CH_3), 2.5 (m, 2, CH_2), 5.0 (m, 1, aliph CH), 7.0 (s, 4 Ar H); ^{19}F NMR δ −74.0, −76.7; ^{13}C NMR δ 20.9 (CH_3), 25.8, 28.0, 34.5 (3 × CH_2), 81.8 (q, J = 31.5 Hz, CCF_3), 122 (q, J = 283 Hz, CF_3), 128.5, 129.4 (arom CH) 136, 137.3 (quatern arom C).

5-(*p*-Methoxyphenyl)-1,1,1-trifluoropentan-2-ol Triflate (1e). The usual treatment with pyridine and triflic anhydride of alcohol **1i** (for preparation of **1i** see below) gave **1e** in 83% yield: ^1H NMR δ 1.9 (m, 4, $(CH_2)_2$), 2.6 (m, 2, CH_2), 3.8 (s, 3, OCH_3), 5.0 (m, 1, aliph CH), 6.9 (m, 4, Ar H); ^{19}F NMR δ −73.3, −76.7; ^{13}C NMR δ 25.9, 28.0, 34.1 (3 × CH_2), 55.3 (MeO), 82.0 (q, J = 34.5 Hz, CCF_3), 114.3 (arom CH), 122.4 (q, J = 282 Hz, CF_3), 129.5 (arom CH), 132.6, 158.5 (quatern arom C).

5-(*p*-Chlorophenyl)-1,1,1-trifluoropentan-2-ol Triflate (1f). Reaction of pyridine, triflic anhydride, and alcohol **1j** (for preparation of **1j** see below) gave triflate **1f** in a quantitative yield: ^1H NMR δ 1.9, 2.7 (br m, 6, $(CH_2)_3$), 5.1 (m, 1, aliph CH), 7.2 (m, 4, Ar H); ^{19}F NMR δ −75, −77.7.

5-(*p*-Methylphenyl)-1,1,1-trifluoropentan-2-ol (1h). Reduction of ketone **4b** with $LiAlH_4$ led to **1h** (yield 95%): ^1H NMR δ 1.5 (m, 4, $(CH_2)_2$), 2.1 (s, 3, CH_3), 2.5 (m, 3, CH_2, OH), 3.8 (m, 1, aliph CH), 7.0 (s, 4, Ar H); ^{19}F NMR δ −80.5 (d, J = 7 Hz); ^{13}C NMR (Table V); high-resolution mass spectrum M^+ 232.1073, calcd for $C_{12}H_{15}OF_3$ 232.1074.

5-(*p*-Methoxyphenyl)-1,1,1-trifluoropentan-2-ol (1i). Reduction of ketone **4c** with $LiAlH_4$ led to **1i** (yield 86%): ^1H NMR δ 1.7 (m, 4, $(CH_2)_2$), 2.2 (br s, 1, OH), 2.6 (m, 2, CH_2), 3.8 (s, 3, OCH_3), 3.9 (br m, 1, aliph CH), 7.0 (m, 4, Ar H); ^{19}F NMR δ −81 (d, J = 7 Hz); ^{13}C NMR (Table V).

5-(*p*-Chlorophenyl)-1,1,1-trifluoropentan-2-ol (1j). The usual reduction with $LiAlH_4$ of ketone **4d** afforded the alcohol **1j** (yield 80%): ^1H NMR δ 1.7 (m, 4, $(CH_2)_2$), 2.6 (m, 3, CH_2, OH), 3.9 (m, 1, aliph CH), 7.2 (m, 4, Ar H); ^{19}F NMR δ −81 (d, J = 7 Hz); ^{13}C NMR (Table V); high-resolution mass spectrum M^+ 252.0530, calcd for $C_{11}H_{12}OF_3Cl$ 252.0529.

Alcohols 2 and 3a. The alcohols **2a–h** and **3a** were obtained by addition of a Grignard reagent to the appropriate ketone under argon in anhydrous ether as solvent. The reaction mixtures, after being heated and refluxed for 2 h, were cooled and hydrolyzed with saturated aqueous ammonium chloride. The usual workup led to the crude alcohols.

2,5-Diphenyl-1,1,1-trifluoropentan-2-ol (2a). The reaction between phenylmagnesium bromide (10 mmol in 25 mL of dry ether) and ketone **4a** (10 mmol in 25 mL of dry ether), followed by distillation (bp 127 °C (0.15 mmHg)), afforded the pure alcohol (yield 86%): ^1H NMR δ 1.6, 2.1, 2.6 (m, 7, $(CH_2)_3$, OH), 7.4 (m, 10, 2 × Ar H); ^{19}F NMR δ −80; ^{13}C NMR (Table V); high-resolution mass spectrum M^+ 294.1233, calcd for $C_{17}H_{17}OF_3$ 294.1232.

5-(*p*-Methylphenyl)-2-phenyl-1,1,1-trifluoropentan-2-ol (2b). Phenylmagnesium bromide (20 mmol) was allowed to react with the **4b** ketone (20 mmol) in dry ether. The crude product, purified by flash chromatography (pentane and pentane + 10% ether), afforded the pure alcohol **2b** in 85% yield: ^1H NMR δ 1.3 (s, 3, CH_3), 1–2.8 (m, 7, $(CH_2)_3$, OH), 7.0 (m, 4, Ar H), 7.4 (m, 5, Ar H); ^{19}F NMR δ −80.5; ^{13}C NMR (Table V); high-resolution mass spectrum M^+ 308.1388, calcd for $C_{18}H_{19}OF_3$ 308.1388.

5-(*p*-Methoxyphenyl)-2-phenyl-1,1,1-trifluoropentan-2-ol (2c) was obtained from the starting ketone **4c** in 87% yield: mp 56.3 °C; ^1H NMR δ 1.9–2.7 (br m, 7, $(CH_2)_3$, OH), 3.7 (s, 3, OMe), 6.9, 7.4 (m, 9, Ar H); ^{19}F NMR δ −81; ^{13}C NMR (Table V); high-resolution mass spectrum M^+ 324.1336, calcd for $C_{18}H_{19}O_2F_3$ 324.1337.

5-(*p*-Chlorophenyl)-2-phenyl-1,1,1-trifluoropentan-2-ol (2d) was obtained from the ketone **4d**, purified by distillation: bp 140 °C (0.1 mmHg); yield 60%; ^1H NMR δ 1.5–2.5 (br m, 7, $(CH_2)_3$, OH), 7.1–7.3 (m, 9, Ar H); ^{19}F NMR δ −81; ^{13}C NMR (Table V); high-resolution mass spectrum M^+ 328.0842, calcd for $C_{17}H_{16}OF_3Cl$ 328.0842.

5-(*m*-Chlorophenyl)-2-phenyl-1,1,1-trifluoropentan-2-ol (2e). The starting ketone **4e** gave **2e** in 96% yield (after purification by flash chromatography): ^1H NMR δ 1.7–2.5 (br m, 7, $(CH_2)_3$, OH), 7.1–7.4 (m, 9, Ar H); ^{19}F NMR δ −81; ^{13}C NMR (Table V).

2-(*p*-Methoxyphenyl)-5-phenyl-1,1,1-trifluoropentan-2-ol (2f) was obtained from the (*p*-methoxyphenyl)magnesium bromide and the ketone **4a** in 90% yield. The alcohol **2f** was purified by flash chromatography: ^1H NMR δ 1.6–2.5 (br m, 6, $(CH_2)_3$), 2.7 (s, 1, OH), 3.7 (s, 3, OCH_3), 6.8, 7.1, 7.4 (m, 9, Ar H); ^{19}F NMR δ −81; ^{13}C NMR (Table V); high-resolution mass spectrum M^+ 324.1337, calcd for $C_{18}H_{19}O_2F_3$ 324.1337.

2-(*p*-Chlorophenyl)-5-phenyl-1,1,1-trifluoropentan-2-ol (2g) was obtained by the action of (*p*-chlorophenyl)magnesium bromide on the ketone **4a**. After distillation (bp 160 °C (0.6 mmHg)), the pure product **2g** was obtained in 80% yield: ^1H NMR δ 2.0–2.5 (m, 6, 3 × CH_2), 3.2 (s, 1, OH), 7.2 (m, 9, Ar H); ^{19}F NMR δ −80.8; ^{13}C NMR (Table V); high-resolution mass spectrum M^+ 328.0842, calcd for $C_{17}H_{16}OF_3Cl$ 328.0842.

2-(*m*-Chlorophenyl)-5-phenyl-1,1,1-trifluoropentan-2-ol (2h). The purification by flash chromatography afforded the pure alcohol in 62% yield: ^1H NMR δ 1.7–2.5 (m, 7, $(CH_2)_3$, OH), 7.3 (m, 9, Ar H); ^{19}F NMR δ −81.0; ^{13}C NMR (Table V); high-resolution mass spectrum M^+ 328.0841, calcd for $C_{17}H_{16}OF_3Cl$ 328.0841.

2-Methyl-5-phenyl-1,1,1-trifluoropentan-2-ol (3a). **3a** was generated by the action of methylmagnesium iodide on ketone **4a**. After the usual procedure, the crude alcohol **3a** (80%) was used without any purification: ^1H NMR δ 1.3 (s, 3, CH_3), 1.7 (m, 4, $(CH_2)_2$), 2.2 (s, 1, OH), 2.7 (br t, 2, CH_2), 7.3 (m, 5, Ar H); ^{19}F NMR δ −83.7; ^{13}C NMR δ 19.8 (CH_3), 24.5, 34.8, 36.1 (3 × CH_2), 73.8 (q, J = 28 Hz, quatern aliph C), 126.1 (Ar CH), 126.8 (q, J

= 285 Hz, CF_3), 128.6 (Ar CH), 142.0 (quatern arom C); high-resolution mass spectrum M^+ 232.1074, calcd for $C_{12}H_{15}OF_3$ 232.1074.

2-Methyl-5-phenyl-1,1,1-trifluoropentan-2-ol Mesylate (3b). Compound **3a** (10 mmol) in dry THF (10 mL) was added dropwise to a stirred solution of pentane-washed NaH (12 mmol) in 10 mL of dry THF. A solution of 15 mmol of methanesulfonyl chloride in 15 mL of dry THF was added slowly through a syringe, and the reaction mixture was stirred overnight at room temperature. After acidic hydrolysis, ether extraction, and removal of the solvents by rotary evaporation, the crude mesylate **3b** was obtained in 54% yield: ^1H NMR δ 1.8 (s, 3, CH_3 on carbon α to CF_3), 2.0 (m, 4, $(CH_2)_2$), 2.7 (br t, 2, CH_2), 3.1 (s, 3, Mes), 7.3 (s, 5, Ar H); ^{13}C NMR δ 18.6 (CH_3 on carbon α to CF_3), 24.8 (CH_3 Mes), 35.0, 35.7, 40.5 (3 × CH_2), 88.7 (q, J = 29.7 Hz, quatern aliph C), 124.2 (q, J = 285 Hz, CF_3), 126.2, 128.4, 128.5 (arom CH), 141.2 (quatern arom C).

2-Methyl-5-phenyl-1,1,1-trifluoropentan-2-ol Triflate (3c). Starting from the alcohol **3a** and using the NaH/trifluoromethanesulfonic anhydride method,[12] we obtained the triflate **3c** in 96% yield: ^1H NMR δ 1.8 (br s, 3, CH_3), 2 (m, 4, $(CH_2)_2$), 2.7 (br t, 2, CH_2), 7.2 (s, 5, Ar H); ^{19}F NMR δ −76.5, −81.0; ^{13}C NMR δ 18.7 (CH_3), 24.8, 35.1, 35.6 (3 × CH_2), 96.0 (q, J = 31 Hz, quatern aliph C), 123.6 (q, J = 284 Hz, CF_3), 126.6, 128.6, 128.8 (arom CH), 141.0 (quatern arom C).

Solvolysis. Solvolyses were carried out in an autoclave immersed in an oil bath at the required temperature. The proportions are described in procedures A, B, and C. At the end of the reaction, the trifluoroacetic acid was evaporated and the reaction mixture was extracted with CH_2Cl_2, washed with $NaHCO_3$ and water until neutral, then dried over $MgSO_4$, evaporated, and purified by chromatography (SiO_2, pentane/ether, 10%).

Procedure A (runs 1–7 and run 16): 1 mmol of the alcohol (or mesylate or triflate or tosylate), 3 mL of trifluoroacetic acid, and 1 mL of trifluoroacetic anhydride.

Run 1. The alcohol **1a** (220 mg, 1 mmol), after being heated for 48 h at 140 °C, was transformed into 235 mg of the corresponding trifluoroacetate **1g** (75%).

5-Phenyl-2-(trifluoroacetoxy)-1,1,1-trifluoropentane (1g): IR (film) 1800 cm^{-1}; ^1H NMR δ 1.8 (m, 4, $(CH_2)_2$), 2.6 (br t, 2, CH_2), 5.35 (m, 1, aliph H), 7.13 (s, 5, Ar H); ^{19}F NMR δ −75.8 (s, $OCOCF_3$), −78.2 (d, J = 6 Hz, CF_3).

Run 2. After being heated for 48 h at 140 °C, 370 mg (1 mmol) of the tosylate **1b** remained unchanged.

Run 3. Triflate **1c** (350 mg, 1 mmol), heated for 48 h at 140 °C, was transformed into 187 mg of the cyclized product **5c** (93%).

1-(Trifluoromethyl)-1,2,3,4-tetrahydronaphthalene (5c): MS, m/e 200 (M^+), 131 ($M^+ - CF_3$), 91; ^1H NMR δ 2.0 (m, 4, $(CH_2)_2$), 2.85 (m, 2, CH_2), 3.6 (m, 1, aliph CH), 7.1 (7, 4, Ar H); ^{19}F NMR δ −67.0 (d, J = 6 Hz); ^{13}C NMR.[17] Anal. Calcd for $C_{11}H_{11}F_3$: C, 66.05; H, 5.54; F, 28.50. Found: C, 65.73; H, 5.43; F, 28.58.

Run 4. Triflate **1d** (365 mg, 1 mmol), being heating for 16 h at 160 °C, afforded, after workup and purification (SiO_2, pentane then ether), 110 mg (51%) of the cyclized product **5d**.

7-Methyl-1-(trifluoromethyl)-1,2,3,4-tetrahydronaphthalene (5d): ^1H NMR δ 2.0 (br m, 4, $(CH_2)_2$), 2.3 (s, 3, CH_3), 2.8 (m, 2, CH_2), 3.5 (m, 1, aliph H), 7.1 (m, 3, Ar H); ^{19}F NMR δ −67.0 (d, J = 6 Hz); ^{13}C NMR;[17] high-resolution mass spectrum M^+ 214.0969, calcd for $C_{12}H_{13}F_3$ 214.0969.

Run 5 and Run 6. Only starting material was recovered when 1 mmol of triflates **1e** (380 mg) and **1f** (384 mg) were heated during 48 h at respectively 110 °C and 160 °C. (At higher temperature, tars began to appear besides starting material.)

Run 7. The alcohol **2a** (294 mg), heated for 15 h at 120 °C, was transformed into 240 mg of tetralin **6a**, purified by filtration on a SiO_2 column using pentane then ether as eluent (yield 87%).

1-Phenyl-1-(trifluoromethyl)-1,2,3,4-tetrahydronaphthalene (6a): MS, m/e 276 (M^+), 207 ($M^+ - CF_3$), 198, 129, 91; ^1H NMR δ 1.80 (m, 2, CH_2), 2.35 (m, 2, CH_2), 2.70 (m, 2, CH_2), 7.30 (s, 9, Ar H); ^{19}F NMR δ −65.3; ^{13}C NMR.[17] Anal. Calcd for $C_{17}H_{15}F_3$: C, 73.90; H, 5.47; F, 20.63. Found: C, 73.84; H, 5.55; F, 19.57.

Run 16. Alcohol **3a** (230 mg), submitted to procedure A, was heated at 140 °C during 15 h. After the usual workup, 318 mg of pure **3d** was isolated (97%).

5-Phenyl-2-(trifluoroacetoxy)-2-(trifluoromethyl)pentane (3d): ^1H NMR δ 1.7 (s, 3, CH_3), 2.0 (br m, 4, 2 × CH_2), 2.6 (t, 2, CH_2), 7.2 (s, 5, Ar H); ^{19}F NMR δ −76.5 (s, $OCOCF_3$), −80.7 (s, CF_3); ^{13}C NMR δ 18.5 (CH_3), 24.9, 33.0, 35.8 (3 × CH_2), 86.9 (q, J = 30 Hz, aliph quatern C), 114.5 (q, J = 286 Hz, $OCOCF_3$), 124.5 (q, J = 284 Hz, CF_3), 126.5, 128.5, 128.7 (arom CH), 141 (arom quatern C), 152 (q, J = 43 Hz, $COCF_3$).

Procedure B (Runs 8–15 and 17). The alcohol (1.5 mmol) and 25 mL of a solution of H_2SO_4 (2 × 10^{-2} M) in trifluoroacetic acid were heated at reflux temperature (72 °C).

To determine cyclization rates, we took samples at different times and monitored the reaction progress by GC (Table IV). Disappearance of the alcohol corresponds to formation of the cyclized product since the cyclization yield is ~90%.

Run 8. Alcohol **2a** (294 mg), submitted to procedure B during $^1/_2$ h, was transformed into **6a**: 285 mg (85%) after purification.

Run 9. Alcohol **2b** (310 mg), heated during $^1/_2$ h, was transformed into **6b**: 246 mg (85%) after purification.

7-Methyl-1-phenyl-1-(trifluoromethyl)-1,2,3,4-tetrahydronaphthalene (6b): ^1H NMR δ 1.4–2.4 (br m, 4, $(CH_2)_2$), 2.1 (s, 3, CH_3), 2.7 (m, 2, CH_2), 7.1 (s, 8, Ar H); ^{19}F NMR δ −65.8; ^{13}C NMR;[17] high-resolution mass spectrum M^+ 290.1281, calcd for $C_{18}H_{17}F_3$ 290.1282.

Run 10. Alcohol **2c** (325 mg) was transformed in 1 h into **6c**: 306 mg after purification (95%).

7-Methoxy-1-phenyl-1-(trifluoromethyl)-1,2,3,4-tetrahydronaphthalene (6c): ^1H NMR δ 1.7–2.7 (m, 6, $CH_2)_3$), 3.65 (s, 3, OMe), 6.8 (m, 3, Ar H), 7.2 (s, 5, Ar H); ^{19}F NMR δ −65.0; ^{13}C NMR;[17] high-resolution mass spectrum M^+ 306.1230, calcd for $C_{18}H_{17}OF_3$ 306.1231.

Run 11. Procedure B applied for 1 h to 328 mg of alcohol **2d** afforded, after the usual workup and purification, 280 mg of **6d** (yield 90%).

7-Chloro-1-phenyl-1-(trifluoromethyl)-1,2,3,4-tetrahydronaphthalene (6d): ^1H NMR δ 1.8, 2.3, 2.8 (3 × CH_2) 7.2 (m, 8, Ar H); ^{19}F NMR δ −66.7; ^{13}C NMR;[17] high-resolution mass spectrum M^+ 310.0738, calcd for $C_{17}H_{14}F_3Cl$ 310.0736.

Run 12. Alcohol **2e** (328 mg) led in $^1/_2$ h to the cyclized product **6e**: 280 mg after purification (90%).

6-Chloro-1-phenyl-1-(trifluoromethyl)-1,2,3,4-tetrahydronaphthalene (6e): ^1H NMR δ 1.7, 2.3, 2.7 (m, 6, 3 × CH_2), 7.13 (s, 8, Ar H); ^{19}F NMR δ −66; ^{13}C NMR.[17,18]

Run 13. Alcohol **2f** (325 mg) gave, in 5 min, 305 mg of the cyclized product **6f** (yield 95% after purification).

1-(*p*-Methoxyphenyl)-1-(trifluoromethyl)-1,2,3,4-tetrahydronaphthalene (6f): ^1H NMR δ 1.7, 2.3, 2.8 (m, 6, 3 × CH_2), 3.8 (s, 3, OCH_3), 7.0 (m, 4, Ar H), 7.2 (m, 4, Ar H); ^{19}F NMR δ −66.8; ^{13}C NMR;[17] high-resolution mass spectrum M^+ 306.1230, calcd for $C_{18}H_{17}OF_3$ 306.1231.

Run 14. **2g** (328 mg) was transformed in 1 h to **6g**: 263 mg (85%) after purification.

1-(*p*-Chlorophenyl)-1-(trifluoromethyl)-1,2,3,4-tetrahydronaphthalene (6g): ^1H NMR δ 1.7, 2.3, 2.8 (m, 6, 3 × CH_2), 7.2 (m, 8, Ar H); ^{19}F NMR δ −65.3; ^{13}C NMR;[17] high-resolution mass spectrum M^+ 310.0738, calcd for $C_{17}H_{14}F_3Cl$ 310.0736.

Run 15. 2h (330 mg) refluxed during 6 h afforded **6h**: 295 mg (95%) after purification.

1-(*m*-Chlorophenyl)-1-(trifluoromethyl)-1,2,3,4-tetrahydronaphthalene (6h): ^1H NMR δ 1.5, 2.2, 2.8 (m, 6, 3 × CH_2), 7.2 (m, 8, Ar H); ^{19}F NMR δ −66.7; ^{13}C NMR;[17] high-resolution mass spectrum M^+ 310.0738, calcd for $C_{17}H_{14}F_3Cl$ 310.0736.

Run 17. Alcohol **3a** (340 mg) heated for 15 h afforded the trifluoroacetate derivative **3d** in 80% yield (see run 16).

Procedure C (runs 18 and 19) was carried out by introduction of 3 mmol of starting material (mesylate or triflate) into a mixture of trifluoroacetic acid (14 mL), trifluoroacetic anhydride (3 mL), and 500 mg of CF_3COONa as buffer.

Run 18. The mesylate **3b** (930 mg), heated during 20 h at 140 °C, led to a mixture of **7**, **8**, and tars; a filtration on SiO_2 with pentane as eluent afforded 43 mg of **7** + **8** (yield in **7** + **8** 20%) (see below).

Run 19. The triflate **3c** (1 g) after being heated for 3 h at 80 °C gave a mixture of products; after filtration, **7** (53 mg, 25%),

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8 (17 mg, 8%), **3a** (46.5 mg, 20%), and polymeric material (45%) were isolated.

5-Phenyl-2-(trifluoromethyl)pent-2-ene (7): MS, *m/e* 214 (M^+), 91; ^1H NMR δ 1.65 (s, 3, CH_3), 2.6 (br m, 4, 2 × CH_2), 6.15 (br m, 1, ethylenic H), 7.2 (s, 5, Ar H); ^{19}F NMR δ −70.3.

5-Phenyl-2-(trifluoromethyl)pent-1-ene (8): MS, *m/e* 214 (M^+), 118, 104, 91; ^1H NMR δ 1.5–2.5 (br m, 4, 2 × CH_2), 2.7 (br t, 2, CH_2), 5.4 (q, J = 1.3 Hz, 1, ethylenic H cis to CF_3), 5.7 (m, 1, ethylenic H trans to CF_3), 7.4 (s, 5, Ar H); ^{19}F NMR δ −69.3; ^{13}C NMR δ 29.2, 35.2 (2 CH_2), 117.6 (q, J = 6 Hz, ethylenic CH_2), 126.1, 128.5 (arom CH), 138.5 (q, J = 29 Hz, ethylenic quatern C), 141.7 (s, arom quatern C).

Procedure D. (Runs 20–22). The solvolysis was carried out with 1.4 g of **3c** (4 mmol) in hexafluoroisopropyl alcohol (10 mL) by using either 1 g of CO_3Na_2 (run 20) or 1 g of CF_3COONa (run 21) as buffer, or no buffer at all (run 22); after being heated for 16 h at 100 °C, the hexafluoroisopropyl alcohol was evaporated and the reaction mixture was extracted with CH_2Cl_2, washed with water, dried, evaporated, and purified by chromatography (SiO_2, pentane and ether).

Run 20. Procedure D afforded 60 mg of **7** (28%), 23 mg of **8** (11%), 49 mg of **3a** (21%), and 38% of polymeric material.

Run 21. Procedure D afforded a mixture of 51 mg of **7** (24%), 30 mg of **8** (14%), 46 mg of **3a** (20%), and 40% of polymeric material.

Run 22. Procedure D afforded a mixture of 43 mg of **8** (20%) and 306 mg of **3e** (80%).

2-(Hexafluoroisopropoxy)-5-phenyl-2-(trifluoromethyl)-pentane (3e): ^1H NMR δ 1.2 (br s, 3, CH_3), 1.7 and 2.7 (br s and br m, 6, 3 × CH_2), 5.8 (m, 1, H *i*-Pr), 7.23 (s, 5, Ar H); ^{19}F NMR δ −74.3 (d, J = 7 Hz, CF_3-*i*-Pr), −83.7 (s, CF_3).

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Registry No. **1a**, 112298-06-3; **1b**, 112298-07-4; **1c**, 112298-08-5; **1d**, 112298-09-6; **1e**, 112298-10-9; **1f**, 112298-11-0; **1g**, 112298-12-1; **1h**, 112298-13-2; **1i**, 112298-14-3; **1j**, 112298-15-4; **2a**, 112298-16-5; **2b**, 112319-75-2; **2c**, 112298-17-6; **2d**, 112298-18-7; **2e**, 112298-19-8; **2f**, 112298-20-1; **2g**, 112298-21-2; **2h**, 112298-22-3; **3a**, 112298-23-4; **3b**, 112298-24-5; **3c**, 112298-25-6; **3d**, 112298-26-7; **3e**, 112298-27-8; **4a**, 85674-68-6; **4b**, 112298-28-9; **4c**, 112298-29-0; **4d**, 112298-30-3; **4e**, 112298-31-4; **5c**, 112298-32-5; **5d**, 112319-76-3; **6a**, 112298-33-6; **6b**, 112298-34-7; **6c**, 112298-35-8; **6d**, 112298-36-9; **6e**, 112298-37-0; **6f**, 112298-38-1; **6g**, 112298-39-2; **6h**, 112298-40-5; **7**, 33501-90-5; **8**, 112298-41-6; 1-bromo-3-(*p*-chlorophenyl)propane, 64473-35-4; 1-bromo-3-(*m*-chlorophenyl)propane, 91085-89-1; 3-(*m*-chlorophenyl)propanol, 22991-03-3; 3-(*p*-chlorophenyl)propanol, 6282-88-8; (*m*-chlorophenyl)magnesium bromide, 36229-42-2; (*p*-methoxyphenyl)magnesium bromide, 13139-86-1; 1-bromo-3-phenylpropane, 637-59-2; 1-bromo-3-(*p*-methylphenyl)propane, 54540-53-3; 1-bromo-3-(*p*-methoxyphenyl)propane, 57293-19-3.

Supplementary Material Available: Table V showing the ^{13}C chemical shifts of the CF_3 alcohols **1a,h–j** and **2a–h** (1 page). Ordering information is given on any current masthead page.

Intramolecular Friedel–Crafts Alkylation and Chloroalkylation of 5-Aryl-1,1,1-trifluoropentan-2-ones. A Route to (Trifluoromethyl)dihydronaphthalenes and (Trifluoromethyl)tetrahydronaphthalenes

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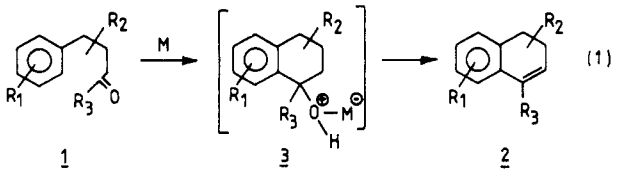
The Friedel–Crafts cyclization of some 5-aryl-1,1,1-trifluoropentan-2-ones yields selectively either 1-(trifluoromethyl)dihydronaphthalenes or 1-chloro-1-(trifluoromethyl)tetrahydronaphthalenes or 1-aryl-1-(trifluoromethyl)tetrahydronaphthalenes, depending on the solvent and the acid.

The Friedel–Crafts cyclization of γ-aryl ketones 1 generally yields 1-substituted 3,4-dihydronaphthalenes **2**,[1] although the product from 5-phenylpentan-2-one (**1a**), (R_1, R_2 = H, R_3 = CH_3) disproportionates under cyclization conditions to a 1:1 mixture of 1-methylnaphthalene and 1-methyl-1,2,3,4-tetrahydronaphthalene[2] (eq 1).



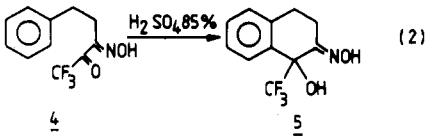
(1)

1 **3** **2**

M = H^+ or Lewis acid

1a, **2a**: R_1 = R_2 = H, R_3 = CH_3

Although it is generally agreed that the intermediate to **2** is the complex **3**, until recently the only reported isolation of the corresponding benzylic alcohol involved the cyclization of the α-trifluoromethyl ketone **4** to give **5**[3] (eq 2).



(2)

4 **5**

In a recent study of the Friedel–Crafts reaction of benzene with 1,1,1-trifluoroacetone, we were able to isolate

† CNRS-CERCOA.

‡ Rhône-Poulenc Santé.

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