ELSEVIER

Journal of Fluorine Chemistry 107 (2001) 301–310

JOURNAL OF FLUORINE CHEMISTRY

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Selective electrochemical synthesis and reactivity of functional benzylic fluorosilylsynthons

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Received 25 April 2000; accepted 11 May 2000

Abstract

Electrochemical reductive silylation of *meta*-(trifluoromethyl)arenes by the sacrificial anode technique selectively led to *meta*-trimethylsilyldifluoromethylarenes ($ArCF_2TMS$), in the presence of an excess of TMSCl and in a THF/cosolvent mixture (cosolvent = DMPU or HMPA). In the case of *meta*-(trimethylsilyldifluoromethyl)trifluoromethylbenzene, the influence of the cosolvent on the silylation selectivity was studied. A cyclic voltammetry study allowed an explanation of the difference in the results obtained between the trifluoromethylbenzene and *meta*-bistrifluoromethylbenzene series. $ArCF_2TMS$ (Ar = Ph, *m*-$CF_3C_6H_4$) species were found efficient for $ArCF_2$-group transfer to diverse electrophiles under Fuchigami's conditions (KF catalysis in DMF).

Keywords: Fluoro-benzylsilanes; Electrosynthesis; Sacrificial aluminium anode; Cyclic voltammetry; Solvent effect; Difluorobenzylation

1. Introduction

The interest of introducing a fluorinated group into a molecular structure has clearly been demonstrated, particularly concerning the modification of its biological properties [1,2]. Consequently, synthons allowing selective access to fluorinated compounds are actively researched as shown, for example, by the numerous papers relative to the use of Ruppert's reagent [3] in anionic trifluoromethylation reactions. As far as we were concerned, we focused our interest on RCF_2-building block synthons; we therefore, reported a molar scale electrosynthesis of $PhCF_2TMS$ (TMS = $SiMe_3$) [4] and $TMSCF_2COOEt$ [5]. We demonstrated the ability of these synthons to transfer the RCF_2-group (R = Ph, COOEt) to carbonyl compounds. We report here the electrosynthesis of *meta*-(difluorotrimethylsilylmethyl)trifluoromethylbenzene (**2**), *meta*-(difluorotrimethylsilylmethyl)phenoxytrimethylsilane (**3**), the corresponding deprotected phenol (**3′**), *meta*-(difluorotrimethylsilylmethyl)-*N*-trimethylsilylaniline (**4**) and the corresponding deprotected aniline (**4′**). A wide range of anionic difluorobenzylation with $PhCF_2TMS$ is described here as well as the reactivity of **2** towards benzaldehyde.

2. Results and discussion

2.1. Electrosilylation of m-bis(trifluoromethyl)benzene (1)

In order to prepare a synthon with two different fluorinated groups (CF_3- and CF_2-) on the same aromatic ring, we found the conditions for the selective reduction of commercially available *m*-bis(trifluoromethyl)benzene, *m*-BTFMB (**1**), in the presence of an excess of trimethylchlorosilane, TMSCl, which led to synthon **2**. To our knowledge, the only present chemical route to **2** implies a photochemical reaction between **1** and hexamethyldisilane [6]; but this reaction was definitely not selective (the benzenic ring being also silylated) and compound **2** was obtained in low yield (26%) Scheme 1.

The remarkable chemo- and regioselectivities of electrosynthesis in organosilicon series[1] encouraged us to apply this technique to the preparation of **2**.

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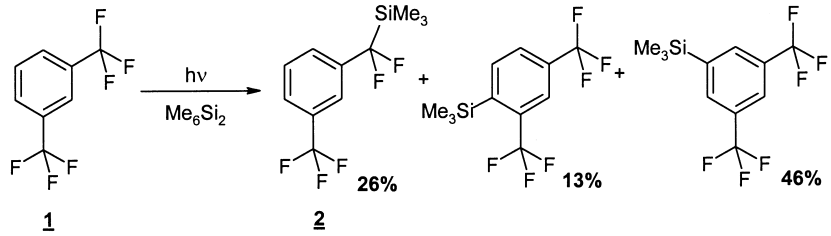
[1] To be published in Rhodia Publications.

0022-1139/01/$ – see front matter
PII: S0022-1139(00)00373-0



Scheme 1. Photochemical silylation of *m*-BTFMB.

Table 1
Trimethylsilylation of *m*-BTFMB with HMPA as the cosolvent

Current passed (F mol^{-1})	**1** (% GC)	**2** (% GC)	**2a** (% GC)	**2b** (% GC)
0.3	90	9	1	0
0.6	80	14	6	0
2.0	40	18	40	0
3.6	0	21	77	0

As we generally proceed for each new reaction, the electrolysis of **1** was first performed with hexamethylphosphoramide (HMPA) as the cosolvent according to Scheme 2.

In Table 1 it is reported that the balance of the reaction according to the current passed, 2 F mol^{-1} being theoretically necessary for the reduction of a C–F bond.

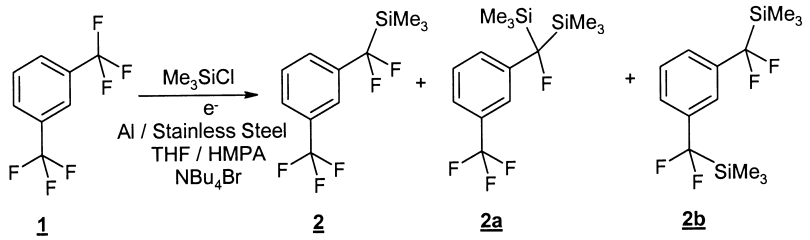
These results lead to two remarks:

- monosilylation was not selective under these conditions: only 60% of **1** were converted when 2 F mol^{-1} were passed whereas disilylation reached 40%;
- disilylation occurred on the benzylic carbon concerned in the first reductive silylation and the gem-disilylation leading exclusively to **2a** largely prevailed after the passage of 3.6 F mol^{-1} (77 versus 21% selectivity for the monosilylation).

To understand these unexpected results, a cyclic voltammetry study was necessary. Indeed, the chemoselectivity of electrosynthesis reactions, even under the intensiostatic mode, depends on the value of the relative reduction potential of each species present in the reaction mixture (the less cathodic compound being the first reduced). So, the successive reduction peak potentials of **1**, **2** and for comparison, those of trifluoromethylbenzene (TFMB) and its monosilylated derivative were measured in several mixtures of THF and cosolvents [7]. As we aimed at finding a way to carry out a selective monosilylation, we report the sole first reduction peak values and the difference between the reduction potentials of the unsilylated substrates and the corresponding monosilylated compounds in four aprotic solvents and solvent mixtures (Tables 2 and 3).

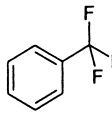
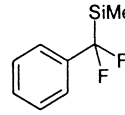
The values found for TFMB were very close to those reported in the literature under different conditions [8,9], the difference $E_1 - E_1'$ is at least 100 mV in all solvents. We had previously shown [10] that the selective monosilylation of *o*-dichlorobenzene required a 200 mV difference. In addition, the preparative silylation of TFMB was performed with HMPA, *N*,*N*′-dimethylpropyleneurea (DMPU) or dimethylformamide (DMF) as cosolvent and a good selectivity was observed for the monosilylation versus disilylation [4]: in this case, 100 mV are sufficient to reach the required selectivity.

Comparing Tables 2 and 3, we can see that the reduction of a C–F bond in **1** or **2** is easier (by about 400 mV) than that observed in the TFMB series. This observation is consistent with an activation due to the second trifluoromethyl group decreasing the LUMO energy of the compound and then making the bis(trifluoromethylated) molecule more easily reducible than the mono substituted one. Furthermore, in THF/HMPA (9:1), as far as compounds **1** and **2** were concerned, an unexpected small difference between E_1 and E_1' (70 mV) was observed: this value could explain the loss of selectivity for the monosilylation of *m*-BTFMB when electrosynthesis was performed in the presence of this cosolvent. The difference $E_1 - E_1'$ being higher with DMPU (140 mV), an electrolysis was performed with DMPU and under these conditions, **2** was obtained with a good conversion (90%) and a reasonable yield (72%) (Table 4).



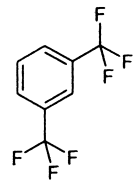
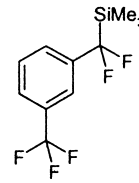
Scheme 2. Electrochemical silylation of *m*-BTFMB.

Table 2
First reduction potential of TFMB and its monosilylated derivative

Solvent	 E_1 (V/SCE)[a] ±0.01	 E'_1 (V/SCE)[a] ±0.01	$E_1 - E'_1$ (mV)	Monosilylated/disilylated after 2 F mol^{-1}
THF	−2.68	−2.68	0	Low conduction
THF/HMPA (9/1)	−2.53	−2.68	150	92/8
THF/DMPU (9/1)	−2.60	−2.70	100	90/5
DMF	−2.50	−2.63	130	95/5

[a] Measured at a 125 μm diameter gold working microelectrode, in a 0.1 M NBu_4PF_6 solution.

Table 3
First reduction potential of **1** and **2**

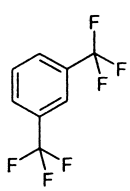
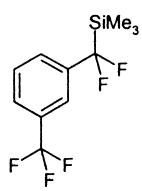
Solvent	 E_1 (V/SCE)[a] ±0.01	 E'_1 (V/SCE)[a] ±0.01	$E_1 - E'_1$ (mV)
THF	−2.16	−2.28	120
THF/HMPA (9/1)	−2.17	−2.24	70
THF/DMPU (9/1)	−2.10	−2.24	140
DMF	−2.07	−2.22	150

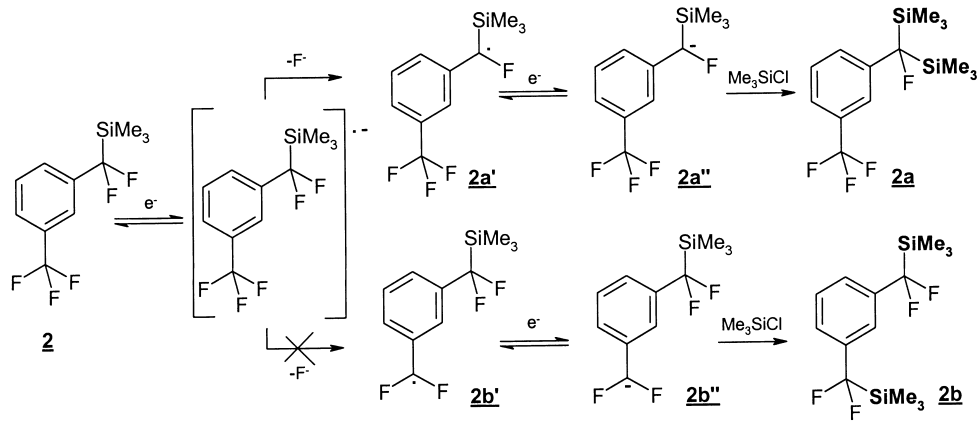
[a] Measured at a 125 μm diameter gold working microelectrode, in a 0.1 M NBu_4PF_6 solution.

Taking into account the gap of 150 mV found between E_1 and E'_1 in DMF, it could have been thought that DMF was suitable to perform the reductive silylation. However, in the case of TFMB, we demonstrated [4,7] that electrolysis in DMF led to the monosilylated compound with excellent selectivity (see Table 2) but with a low conversion because of the reduction of the amide itself, favoured by the electrophilic assistance of TMSCl. For this reason, DMF was not used for the synthesis of **2**.

The electrochemical analytical study points out that the nature of the cosolvent is of great importance to reach the desired selectivity and that DMPU was found to be the best cosolvent for the monosilylation of *m*-BTFMB. On the contrary, HMPA appears to be the most suitable cosolvent to perform the disilylation; it must be noted, that only the first reduction potential value is significantly modified when changing the cosolvent. However, the interpretation of these results is not easy; indeed, until now, the reduction mechanism of benzylic fluorocompounds has not been specifically studied. According to Saveant's paper [11] concerning the electrochemical reductive cleavage of arylmethyl chlorides and bromides, two hypothesis are to be considered: (i) with a stepwise mechanism, an intermediate radical-anion would be formed, followed by carbon–fluorine bond breaking, favoured by strong withdrawing groups such as the nitro group; (ii) with a concerted electron transfer-bond breaking mechanism, the radical would be formed directly as in the case of unsubstituted benzyl chloride and bromide [11]. Thus, the reduction of TFMB would probably take place via the latter mechanism. As far as compound **1** is concerned, we think that the reduction occurs following a stepwise mechanism because the presence of the second CF_3 group,

Table 4
Monosilylation of *m*-BTFMB with DMPU as the cosolvent

Current passed (F mol^{-1})	 (% GC)	 (% GC)	 (% GC)	 (% GC)
1.4	40	53	3	0
2.4	10	72	13	0



Scheme 3. Regioselectivity of the disilylation.

lowering the energy of the π^* orbital of the aromatic moiety, stabilises the radical-anion. In this case, as shown by Saveant [11], the main factor governing the thermodynamics and the kinetics of the reductive cleavage is then the dissociation energy of the bond being broken. Two other groups [12,13] have shown that the solvent nature could modify the cleavage reaction rate; for our part, researches are in progress to verify our hypothesis concerning the reduction mechanism of **1**. The solvent effect could then be interpreted taking into account the additional stabilisation brought by the Mg^{2+} cation associated with the radical-anion, ion pairs being tighter in DMPU than in HMPA.

From **2**, the stabilisation of radicals [14–16] and anions [17,18] by the α-silyl group (Scheme 3) could be a more important factor than the solvent effect for the cleavage of the C–F bond of the radical-anion; thus, differences between reduction potentials measured in HMPA or DMPU would be minimised. When disilylation occurs, only the gem-disilylated product is obtained. The stabilisation of the intermediates (α-silylradical **2a′** and α-silylanion **2a″**) by the trimethylsilyl group, compared to the destabilisation of **2b″** by the +I π effect [19] of the two fluorine atoms could explain the exclusive breaking of the C–F bond of the difluorotrimethylsilylmethyl group (Scheme 3).

2.2. Reactivity of benzylic silyldifluorosynthons

We previously reported the reactivity of $PhCF_2TMS$ towards carbonyl compounds using a F^- catalysis, with tetrabutylammonium fluoride (TBAF) [4]. However, the yields were medium to low, due to the faster hydrolysis of the silylsynthon by the water contained in TBAF solution [7]; we report here new results (Scheme 4 and Table 5) concerning the transfer of difluoromethylarene groups from $PhCF_2TMS$ and from **2** under Fuchigami's conditions [19].

If wanted, all the alcohols can be isolated in their protected form; most of them have never been described previously. With the less reactive electrophiles (phenylethylketone and cyclohexanone) the yields remain low but could be increased using an excess of electrophile [20]. The reactivity of **2** was only tested towards benzaldehyde; compared to $PhCF_2SiMe_3$, the presence of an additional CF_3 group in **2** enhances the reactivity of this compound, the reaction rate being, under the same conditions, four times greater with an excellent isolated yield (80%).

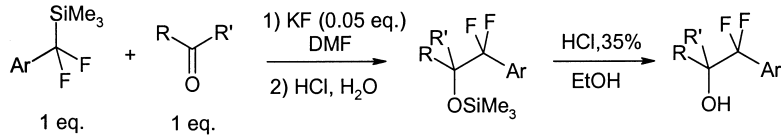
2.3. Electrosilylation of m-(trifluoromethyl)phenol and m-(trifluoromethyl)aniline

The reaction was performed in HMPA according to Scheme 5.

As both compounds include an acidic hydrogen, the first electrochemical reaction which occurs is the reduction (with H_2 evolution) of HCl previously formed in the *O*- or *N*-silylation step. The obtained results are summarised in Table 6, after having passed 3.2 F mol^{-1}.

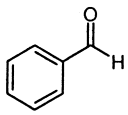
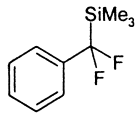
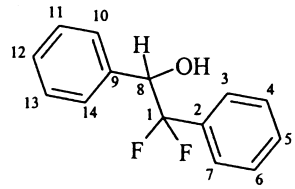
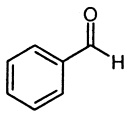
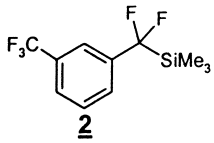
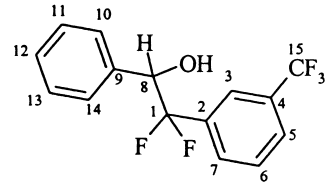
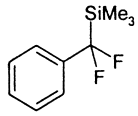
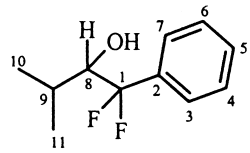
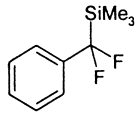
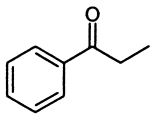
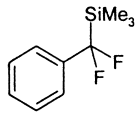
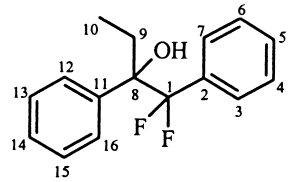
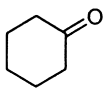
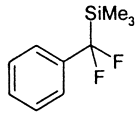
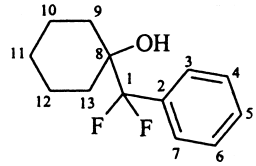
It must be noted that the hydrolysis of the reaction mixture by a saturated $NaHCO_3$ solution allowed stabilisation of the *O*- or *N*-trimethylsilyl derivatives which are much more stable than the corresponding phenol or aniline.

On the other hand, replacing HMPA by DMPU led to non-reproducible results with the amine and to moderate



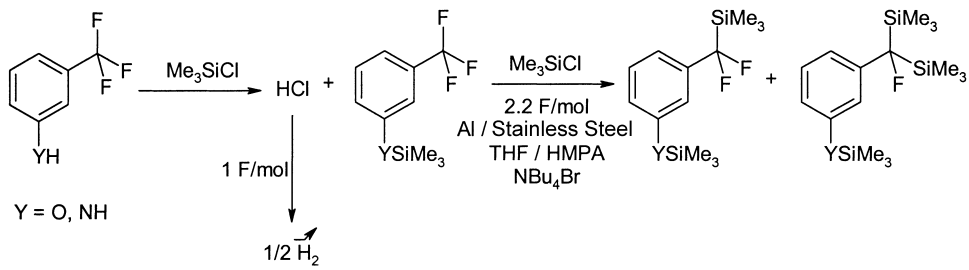
Scheme 4. Reactivity of benzylic silyldifluorosynthons.

Table 5
Transfer of $ArCF_2$ moieties to aldehydes and ketones

Electrophile	$ArCF_2TMS$	Alcohol	Yield %
			73[a]
	 **2**		80[a]
			60[a]
			60[b]
			33[b]
			24[a]

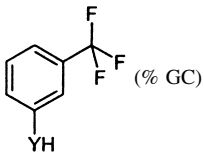
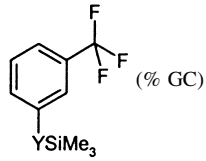
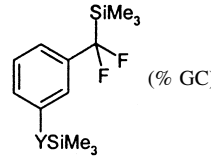
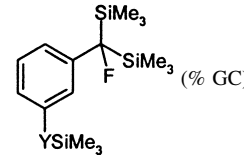
[a] Isolated yield.
[b] Determined by ^{19}F NMR.

yields with *m*-trifluoromethyl phenol after having passed 3.8 F mol^{-1} conversion was only 48% but with a good chemoselectivity (94%); the low faradaic yield can be explained by the very cathodic value of the reduction potential due to the presence of a strong donating group on the aromatic ring. In such a case, HMPA is a better cosolvent than DMPU because of its wider cathodic potential window.



Scheme 5. Electrosilylation of *m*-(trifluoromethyl)phenol and aniline.

Table 6
Electrosilylation of *m*-trifluoromethylphenol and aniline after 3.2 F mol^{-1}

Y	 (% GC)	 (% GC)	 (% GC)	 (% GC)
O	0	5	89	5
NH	0	2	93	4

3. Conclusion

These results constitute a new example of the potentiality of electrosynthesis for regioselective reactions from polyfunctional compounds; moreover, we found an unexpected solvent effect on the selectivity of the silylation which could be correlated to the modification of the reduction potential values according to the solvent mixture. We also report optimised conditions for transferring difluoro building blocks to electrophiles.

4. Experimental

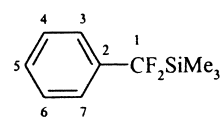
4.1. Materials

For electrolysis in a 70 ml cell, THF (SDS) was distilled over sodium-benzophenone ketyl. The cosolvents HMPA (Lancaster), DMPU (Fluka), TDA-1 (Aldrich) were used without any treatment. The supporting electrolytes were pumped off during 48 h at room temperature. Trimethylchlorosilane was distilled over Mg powder just before use. Gas chromatography was performed with a temperature-programmable Hewlett-Packard 5890A apparatus equipped with a 25 m × 0.25 μm CP-Sil 5CB capillary column. ^{1}H NMR spectra were recorded in $CDCl_3$ at 250 MHz with a Brucker AC 250 spectrometer, using residual $CHCl_3$ ($\delta = 7.27$ ppm) as the internal standard. ^{13}C NMR spectra were obtained at 62.86 MHz with a Brucker AC 250 using $CDCl_3$ ($\delta = 77.70$ ppm) as the internal standard. The signals for ^{1}H and ^{13}C NMR are designated s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet). ^{29}Si NMR spectra were recorded in $CDCl_3$ at 39.73 MHz with a Brucker AC 200 spectrometer and were referenced to TMS. ^{19}F NMR spectra were recorded in $CDCl_3$ at 282 MHz with a Brucker AC 200 spectrometer and were referenced to $CFCl_3$ using $PhOCF_3$ ($\delta = -58.3$ ppm) as the internal standard. Electron impact mass spectra were recorded at an ionisation voltage of 70 eV with a VG Micromass 16F spectrometer coupled with a gas chromatograph equipped with a 25 m × 0.25 μm CP-Sil capillary column. IR spectra were recorded with a Perkin–Elmer 1420 spectrophotometer in pure liquid films (NaCl discs). Elementary microanalysis were performed by the ''Service Central de Microanalyses'' of CNRS (France). Solvents, $PhCF_3$, *m*-$F_3CC_6H_4CF_3$, KF were purchased from Aldrich and SiO_2 (9385) from Merck. *m*-$F_3CC_6H_4NH_2$ and *m*-$F_3CC_6H_4OH$ were provided by Rhodia Chimie.

4.2. Electrosynthesis of trimethylsilyldifluoromethylarenes, $ArCF_2TMS$, in a 70 ml laboratory cell

The electrolysis of magnetically stirred solutions was performed under nitrogen, in a previously described undivided cell fitted with an aluminium rod as the anode and a concentric cylindrical stainless steel grid as the cathode. These two electrodes were previously chemically scored by a 10% HCl solution, then rinsed out several times with distilled water and with acetone. The oven dried cell containing the supporting electrolyte, NBu_4Br (0.25 g, 0.8 mmol) was deaerated twice under vacuum and then with dry nitrogen gas. THF (55 ml), DMPU (1.8 ml, 14.9 mmol) or HMPA (3.2 ml, 14.9 mmol) and TMSCl (9 ml, 68.5 mmol) were introduced under a low stream of nitrogen. HCl resulting from the reaction between TMSCl and the residual water was removed by pre-electrolysing the solution ($i = 0.1$ A; $j = 0.4$ A dm^{-2}). The other hydrolysis product, Me_6Si_2O, remains electrochemically inert. When evolution of H_2 ceased, the substrate $ArCF_3$ (13.7 mmol) was introduced through a septum by syringe. The electrolysis was then performed ($i = 0.1$ A; $j = 0.4$ A dm^{-2}) over 9 h, until the required charge (2.4 F mol^{-1}) has been passed. The progress of the reaction was monitored by gas chromatography. At the end of the electrolysis, the mixture was poured into 250 ml of cold water. The organic layer was extracted three times with Et_2O (100 ml) and washed twice with cold water (100 ml). After drying over $MgSO_4$, Et_2O was evaporated off. Fractional distillation over a Vigreux column was then performed to recover the pure product.

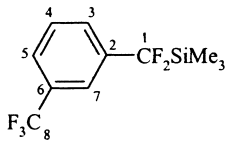
4.3. Trimethylsilyldifluoromethylbenzene



CAS number: 149021-01-2; $M = 200.31$ g mol^{-1}; colourless liquid; $Eb_{20} = 80$°C.

^{1}H NMR: δ_H 0.21 ppm (s, 9H, TMS), δ_H 7.26–7.45 ppm (m, 5H, Ph); ^{13}C NMR: δ_C −4.9 ppm (s, TMS), $\delta_{C3,C7}$ 124.7 ppm (t, $^3J_{C-F} = 8.0$ Hz), δ_{C5} 128.3 ppm (s), $\delta_{C4,C6}$ 128.8 ppm (t, $^4J_{C-F} = 2.6$ Hz), δ_{C1} 134.5 ppm (t, $^1J_{C-F} = 265.0$ Hz), δ_{C2} 138.3 ppm (t, $^2J_{C-F} = 20.4$ Hz); ^{19}F NMR: δ_F −112.5 ppm (s); ^{29}Si NMR: δ_{Si} 4.3 ppm (t, $^2J_{Si-F} = 34.7$ Hz); IR: 2965, 1954, 1878, 1812, 1754, 1449, 1253, 1234, 1080, 989; MS: m/z: 185 $(M-15)^+$, 127 $(M-73)^+$, 108 $(M-92)^+$, 93 $(M-107)^+$, 77 ($SiFMe_2^+$), 73 ($SiMe_3^+$); anal. calcd (found) for $C_{10}H_{14}SiF_2$: C% = 59.96 (58.12), H% = 7.04 (7.04), F% = 18.97 (19.00).

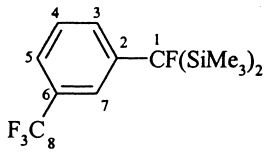
4.4. m-(Trimethylsilyldifluoromethyl)trifluoromethylbenzene



$M = 268.31$ g mol^{-1}; colourless liquid; $Eb_5 = 60$°C.

^{1}H NMR: δ_H 0.16 ppm (s, 9H, TMS), δ_H 7.53–7.67 ppm (m, 4H, Ar); ^{13}C NMR: δ_C −5.2 ppm (t, $^3J_{C-F} = 1.9$ Hz, TMS), δ_{C7} 121.6 ppm (m), δ_{C5} 125.6 ppm (m), δ_{C8} 125.4 ppm (q, $^1J_{C-F} = 263.9$ Hz), δ_{C1} 126.1 ppm (t, $^1J_{C-F} = 264.2$ Hz), δ_{C3} 128.1 ppm (t, $^3J_{C-F} = 7.6$ Hz), δ_{C4} 128.9 ppm (s), δ_{C6} 131.0 ppm (q, $^2J_{C-F} = 32.4$ Hz), δ_{C2} 139.4 ppm (t, $^2J_{C-F} = 21.0$ Hz); ^{19}F NMR: δ_{F1} −112.7 ppm (s, 2F), δ_{F8} −62.7 ppm (s, 3F); ^{29}Si NMR: δ_{Si} 5.2 ppm (t, $^2J_{Si-F} = 37.1$ Hz); IR: 2964, 1445, 1335, 1255, 1219, 1170, 1132, 1104, 1076; MS: m/z (relative intensity): 249 $(M-19, 7)$, 195 $(M-73, 7)$, 176 $(M-92, 100)$, 153 (16), 126 (12), 107 (8), 81 (14), 77 (14), 73 (68), 45 (22); anal. calcd (found) for $C_{11}H_{13}SiF_5$: C% = 49.24 (49.18), H% = 4.88 (5.12), F% = 35.41 (33.62).

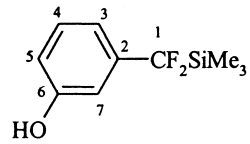
4.5. m-(Bistrimethylsilylfluoromethyl)trifluoromethylbenzene



$M = 322.51$ g mol^{-1}; colourless liquid; $Eb_5 = 102$°C.

^{1}H NMR: δ_H 0.09 ppm (s, 18H, TMS), δ_H 7.34–7.49 ppm (m, 4H, Ar); ^{13}C NMR: δ_C −2.6 ppm (d, $^3J_{C-F} = 3.8$ Hz, TMS), δ_{C1} 99.7 ppm (d, $^1J_{C-F} = 158.3$ Hz), δ_{C7} 117.8 ppm (m), δ_{C5} 120.8 ppm (q, $^3J_{C-F} = 3.8$ Hz), δ_{C8} 124.4 ppm (q, $^1J_{C-F} = 271.8$ Hz), δ_{C3} 124.8 ppm (d, $^3J_{C-F} = 3.6$ Hz), δ_{C4} 128.3 ppm (s), δ_{C6} 130.2 ppm (q, $^2J_{C-F} = 31.0$ Hz), δ_{C2} 145.8 ppm (d, $^2J_{C-F} = 13.4$ Hz); ^{19}F NMR: δ_{F1} −216.9 ppm (s, 1F), δ_{F8} −63.0 ppm (s, 3F); ^{29}Si NMR: δ_{Si} 4.74 ppm (d, $^2J_{Si-F} = 23.1$ Hz); IR: 2960, 1427, 1329, 1253, 1165, 1128, 1075; MS: m/z (relative intensity): 322 $(M)^+$(<1), 303 $(M-15, 12)$, 230 (77), 215 (13), 203 (48), 189 (13), 188 (14), 153 (36), 133 (71), 115 (10), 101 (8), 77 (100), 73 (81), 59 (19), 45 (26); anal. calcd (found) for $C_{14}H_{22}F_4Si_2$: C% = 52.14 (51.48), H% = 6.88 (6.94), F% = 24.19 (23.87).

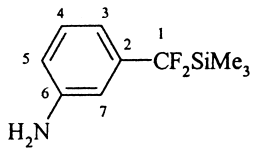
4.6. m-Trimethylsilyldifluoromethylphenol



$M = 216.31$ g mol^{-1}; $Eb_5 = 118$°C (phenol + phenoxy TMS mixture, the isolated phenol decomposed at 45°C).

^{1}H NMR: δ_H 0.14 ppm (s, 9H, TMS), δ_H 5.80 ppm (s, OH), δ_H 6.83–7.30 ppm (m, 4H, Ar); ^{13}C NMR: δ_C −4.8 ppm (t, $^3J_{C-F} = 1.9$ Hz, TMS), δ_{C3} 111.7 ppm (t, $^3J_{C-F} = 8.1$ Hz), δ_{C4} 115.9 ppm (t, $^4J_{C-F} = 2.4$ Hz), δ_{C7} 117.1 ppm (t, $^3J_{C-F} = 7.6$ Hz), δ_{C5} 129.7 ppm (s), δ_{C1} 130.2 ppm (t, $^1J_{C-F} = 265.0$ Hz), δ_{C2} 140.0 ppm (t, $^2J_{C-F} = 20.0$ Hz), δ_{C6} 155.6 ppm (s); ^{19}F NMR: δ_F −112.1 ppm (s); ^{29}Si NMR: δ_{Si} 4.4 ppm (t, $^2J_{Si-F} = 38.2$ Hz); IR: 3379, 2960, 1578, 1449, 1332, 1253, 1172, 1079; MS: m/z (relative intensity): 216 (M^+, 37), 143 $(M-73, 10)$, 124 (92), 103 (20), 96 (56), 77 (42), 73 (100), 45 (23).

4.7. m-Trimethylsilyldifluoromethylaniline



$M = 215.327$ g mol^{-1}.

^{1}H NMR: δ_H 0.15 ppm (s, 9H, TMS), δ_H 5.60 ppm (s, 2H, NH_2), δ_H 6.65–7.27 ppm (m, 4H, Ar); ^{13}C NMR: δ_C −4.8 ppm (t, $^3J_{C-F} = 1.9$ Hz, TMS), δ_{C3} 111.1 ppm (t, $^3J_{C-F} = 8.6$ Hz), δ_{C4} 115.6 ppm (t, $^4J_{C-F} = 2.9$ Hz), δ_{C7} 117.2 ppm (t, $^3J_{C-F} = 7.2$ Hz), δ_{C5} 129.7 ppm (s), δ_{C1} 128.4 ppm (t, $^1J_{C-F} = 265.1$ Hz), δ_{C2} 139.4 ppm (t, $^2J_{C-F} = 20.0$ Hz), δ_{C6} 146.4 ppm (s); ^{19}F NMR: δ_F −112.2 ppm (s); ^{29}Si NMR: δ_{Si} 4.4 ppm (t, $^2J_{Si-F} = 38.5$ Hz); IR: 3368, 2961, 1624, 1594, 1495, 1468, 1457, 1341, 1253, 1124, 1077; MS: m/z (relative intensity): 215 (M^+, 53), 142 ($M-SiMe_3$, 12), 123 (79), 122 (88), 96 (23), 77 (29), 73 (100), 65 (12), 45 (21).

4.8. Cyclic voltammetry procedure

Measurements were carried out with an Electrokemat potentiostat using the interrupt method to minimise the

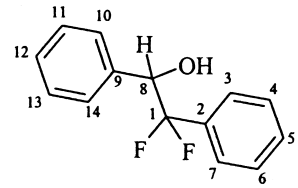
uncompensated resistance (IR) drop. Electrochemical experiments were performed at room temperature in an airtight three-electrode cell connected to vacuum argon/N_2 line. The reference electrode was a saturated calomel electrode (SCE) separated from the non-aqueous solution by a bridge compartment. The counter electrode was a Pt wire spiral of ca. 1 cm^2 apparent surface area, 8 cm long and 0.5 mm diameter. The working electrode was an Au disk of 125 μm diameter. THF (Riedel de Haehn, extra pure) was purified by the previously described method and was stored over 4 Å molecular sieves before use. The supporting electrolyte was Bu_4NPF_6 (Fluka electrochemical grade), used as received. All solutions measured were 0.6–1.10^{-3} M in the organic compound and 0.1 M in supporting electrolyte. Under the same conditions, ferrocene was oxidised at $E^o = 0.51$ V.

4.9. General procedure for anionic aryldifluoromethylation

KF (30 mg, 0.05 equivalent), DMF (5 ml) and the electrophile (10 mmol) were charged, in that order, in a 25 ml round bottomed flask, under nitrogen. $ArCF_2TMS$ (10 mmol) was then added in one portion at room temperature. The reaction mixture was stirred over a period of either 18 to 24 h at room temperature or 2 to 6 h at 70 to 100°C for hindered electrophiles. The reaction mixture was finally poured into 20 ml of aqueous acidic solution (HCl, 1%) and left under efficient agitation for 15 min. The resulting solution was extracted three times with diethyl ether (3 × 10 ml) and the organic phase was washed with brine (10 ml), with an iced saturated bicarbonate aqueous solution (10 ml) and last with brine (10 ml). The ethereal phase was dried with $MgSO_4$ and concentrated under vacuum. The crude product was finally obtained as a mixture of two major products, the *O*-silylated alcohol and the deprotected alcohol, in the minimum ratio of 9/1 in favour of the protected alcohol.

For the deprotection reaction, ethanol (10 ml) and HCl 35% (0.2 ml) were charged in a 25 ml round bottomed flask. The *O*-silylated alcohol was then slowly added and a strong stirring was maintained over a period of 1 h. In the case of tertiary alcohols, we increased the reaction time up to 10 h. More efficient deprotection conditions like a stoichiometric amount of fluoride (TBAF) in THF or citric acid in methanol could also be used. At the end of the stirring period, water was added (20 ml). The resulting medium was extracted three times with diethyl ether (3 × 10 ml) and the organic phase was washed with brine (10 ml), with an iced saturated bicarbonate aqueous solution (10 ml) and last with brine (10 ml). The ethereal phase was dried with $MgSO_4$ and concentrated under vacuum. The product was isolated by column chromatography on silica gel eluting with light petroleum ether and ethyl acetate (95/5 to 90/10).

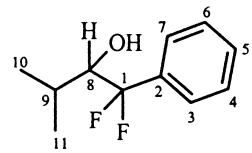
4.10. 1,2-Diphenyl-2,2-difluoroethanol



CAS number: 1494-20-8; $C_{14}H_{12}OF_2$; $M = 234$ g mol^{-1}; white solid; F = 90°C.

^{1}H NMR: δ_H 2.83 ppm (d, 1H, $J_{H-OH} = 10.0$ Hz, OH), δ_{H8} 5.07 ppm (td, 1H, $^3J_{H-F} = 10.0$ Hz), δ_H 7.25–7.48 ppm (m, 10H, Ph); ^{13}C NMR: δ_{C8} 76.9 ppm (t, $^2J_{C-F} = 30.9$ Hz), δ_{C1} 121.1 ppm (t, $^1J_{C-F} = 248.3$ Hz), $\delta_{C3,C7}$ 126.3 ppm (t, $^3J_{C-F} = 6.5$ Hz), δ_{C5} 127.79 ppm (s), $\delta_{C4,C6}$ 127.87 ppm (s), $\delta_{C11,C13}$ 127.92 ppm (s), δ_{C12} 128.6 ppm (s), $\delta_{C10,C14}$ 130.0 ppm (t, $^4J_{C-F} = 1.5$ Hz), δ_{C2} 134.3 ppm (t, $^2J_{C-F} =$ 25.9 Hz), δ_{C9} 135.8 ppm (t, $^3J_{C-F} = 2.3$ Hz); ^{19}F NMR: δ_F −106.7 ppm (d, $^3J_{H-F} = 9.5$ Hz); IR: 3431, 2931, 2852, 1945, 1891, 1823, 1764, 1450, 1254, 1160, 1062; MS: m/z (relative intensity): 234 (M^+, 5), 214 (M−HF, <1), 127 ($PhCF_2$, 26), 107 (Ph-CHOH, M−127, 100), 105 (PhCO, 8), 90 (PhCH, 4), 79 (CF_2CHO, 54), 77 (Ph, 39), 51 (CF_2H, 16); high resolution MS: $M = 234.085622$ (234.085737, −0.5 ppm).

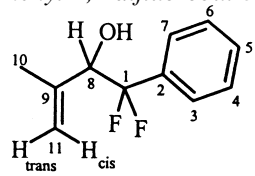
4.11. 3-Methyl-1-phenyl-1,1-difluorobutan-2-ol



$C_{11}H_{14}OF_2$; $M = 200.23$ g mol^{-1}; colourless oil.

^{1}H NMR: δ_{H11} 0.96 ppm (d, 3H), δ_{H10} 1.01 ppm (d, 3H), δ_{H9} 1.78–1.90 ppm (hd, 1H), δ_H 2.21 ppm (s, 1H, OH), δ_{H8} 3.79 ppm (td, 1H, $^3J_{H-F} = 11.5$ Hz), δ_H 7.43–7.56 ppm (m, 5H, Ph); ^{13}C NMR: δ_{C11} 16.5 ppm (s), δ_{C10} 20.7 ppm (s), δ_{C9} 28.4 ppm (t, $^3J_{C-F} = 1.9$ Hz), δ_{C8} 78.3 ppm (t, $^2J_{C-F} = 28.0$ Hz), δ_{C1} 122.2 ppm (t, $^1J_{C-F} = 247.0$ Hz), $\delta_{C3,C7}$ 125.7 ppm (t, $^3J_{C-F} = 6.3$ Hz), $\delta_{C4,C6}$ 128.4 ppm (s), δ_{C5} 130.0 ppm (s), δ_{C2} 135.2 ppm (t, $^2J_{C-F} =$ 25.3 Hz); ^{19}F NMR: δ_F −105.3 ppm (d, 2F, $^3J_{H-F} =$ 11.5 Hz); IR: 3425, 2966, 2879, 1959, 1887, 1813, 1712, 1452, 1261, 1187, 1116, 1054, 1031; MS: m/z (relative intensity): 200 (M^+, 3), 138 (7), 129 (11), 128 (84), 127 (58), 110 (11), 109 (21), 78 (8), 77 (21), 73 (M−127, 100), 72 (13), 55 (48), 43 (30); high resolution MS: $M = 200.101272$ (200.101335, −0.3 ppm).

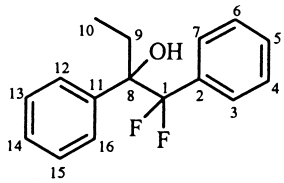
4.12. 3-Methyl-1-phenyl-1,1-difluorobut-3-en-2-ol



$C_{11}H_{12}OF_2$; $M = 198.22$ g mol^{-1}; colourless oil.

^{1}H NMR: δ_{H10} 1.72 ppm (s, 3H), δ_H 2.42 ppm (s, 1H, OH), δ_{H8} 4.48 ppm (t, 1H), $\delta_{H11trans}$ 4.92 ppm (s, 1H), δ_{H11cis} 5.02 ppm (s, 1H), δ_H 7.33–7.56 ppm (m, 5H, Ph); ^{13}C NMR: δ_{C10} 19.1 ppm (s), δ_{C8} 77.8 ppm (t, $^2J_{C-F} = 29.5$ Hz), δ_{C11} 116.6 ppm (s), δ_{C1} 121.2 ppm (t, $^1J_{C-F} = 247.2$ Hz), $\delta_{C3,C7}$ 126.1 ppm (t, $^3J_{C-F} = 6.2$ Hz), $\delta_{C4,C6}$ 128.1 ppm (s), δ_{C5} 130.2 ppm (s), δ_{C2} 134.6 ppm (t, $^2J_{C-F} = 22.9$ Hz), δ_{C9} 141.6 ppm (t, $^3J_{C-F} = 1.9$ Hz); ^{19}F NMR: δ_F −106.2 ppm (d, 2F, $^3J_{H-F} = 11.5$ Hz); IR: 3431, 3068, 3038, 2976, 2930, 1959, 1891, 1813, 1716, 1651, 1608, 1452, 1267, 1168, 1057; MS: m/z (relative intensity): 178 (M^+, 49), 163 (M−15, 6), 127 (90), 109 (6), 77 (21), 71 (M−127, 100).

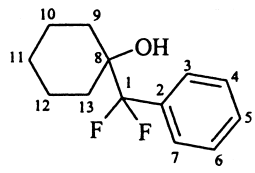
4.13. 1,2-Diphenyl-1,1-difluorobutan-2-ol



$C_{16}H_{16}OF_2$; $M = 262.31$ g mol^{-1}.

^{1}H NMR: δ_{H10} 0.77 ppm (t, 3H), δ_H 2.10 ppm (m, 1H, OH), δ_{H9} 2.40 ppm (m, 2H), δ_H 7.27–7.59 ppm (m, 10H, Ph); ^{13}C NMR: δ_{C9} 7.1 ppm (s), δ_{C10} 27.3 ppm (t, $^3J_{C-F} = 1.9$ Hz), δ_{C8} 79.9 ppm (t, $^2J_{C-F} = 28.1$ Hz), δ_{C1} 122.6 ppm (t, $^1J_{C-F} = 253.1$ Hz), $\delta_{C3,C7}$ 127.1 ppm (t, $^3J_{C-F} = 6.7$ Hz), δ_{C5} 127.2 ppm (s), $\delta_{C4,C6}$ 127.3 ppm (s), $\delta_{C13,C15}$ 128.0 ppm (s), δ_{C14} 128.6 ppm (s), $\delta_{C12,C16}$ 129.5 ppm (t, $^4J_{C-F} = 1.9$ Hz), δ_{C2} 134.2 ppm (t, $^2J_{C-F} = 26.6$ Hz), δ_{C11} 138.0 ppm (t, $^3J_{C-F} = 3.1$ Hz); ^{19}F NMR: δ_{FA} −106.1 ppm (d, 1F, $^2J_{FA-FB} = 245.3$ Hz), δ_{FB} −108.4 ppm (d, 1F, $^2J_{FA-FB} = 245.3$ Hz); IR: 3484, 2977, 1963, 1900, 1816, 1449, 1276, 1221, 1053; MS: m/z (relative intensity): 262 (M^+, <1), 135 (M−127, 100), 127 (14), 105 (13), 91 (5), 77 (21), 57 (55), 29 (21); high resolution MS: $M = 262.116922$ (262.111389, +21.1 ppm).

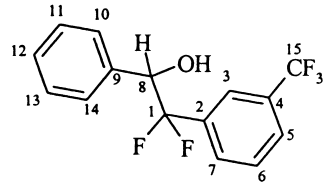
4.14. 2-Phenyldifluoromethylcyclohexanol



$C_{13}H_{16}OF_2$; $M = 226.27$ g mol^{-1}; white solid; F = 76°C.

^{1}H NMR: δ_{H9-13} 1.62 ppm (m, 10H), δ_H 2.02 ppm (s, 1H, OH), δ_H 7.39–7.52 ppm (m, 5H, Ph); ^{19}C NMR: $\delta_{C12,C10}$ 20.7 ppm (s), δ_{C11} 25.6 ppm (s), $\delta_{C9,C13}$ 30.3 ppm (t, $^3J_{C-F} = 2.2$ Hz), δ_{C8} 74.4 ppm (t, $^2J_{C-F} = 27.7$ Hz), δ_{C1} 122.9 ppm (t, $^1J_{C-F} = 249.4$ Hz), $\delta_{C3,C7}$ 127.1 ppm (t, $^3J_{C-F} = 6.7$ Hz), $\delta_{C4,C6}$ 127.3 ppm (s), δ_{C5} 129.6 ppm (s), δ_{C2} 134.2 ppm (t, $^3J_{C-F} = 26.7$ Hz); ^{19}F NMR: δ_F −111.4 ppm (s); IR: 3421, 2940, 1960, 1886, 1808, 1769, 1450, 1278, 1185, 1146, 1043, 984; MS: m/z (relative intensity): 226 (M^+, <1), 127 ($PhCF_2$, 23), 99 (C_6H_{10}-OH, M−127, 100), 81 (C_6H_9, 44); high resolution MS: $M = 226.117561$ (226.116922, −2.8 ppm).

4.15. 1-Phenyl-2-(m-trifluoromethylphenyl)-2,2-difluoroethanol



$C_{15}H_{11}OF_5$; $M = 302.26$ g mol^{-1}; colourless oil.

^{1}H NMR: δ_H 2.76 ppm (s, 1H, OH), δ_{H8} 5.10 ppm (t, 1H, $^3J_{H-F} = 9.2$ Hz), δ_H 7.20–7.73 ppm (m, 9H, Ar); ^{13}C NMR: δ_{C8} 76.6 ppm (t, $^2J_{C-F}$ 31.0 Hz), δ_{C1} 120.6 ppm (t, $^1J_{C-F} =$ 248.9 Hz), δ_{C15} 123.7 ppm (q, $^1J_{C-F} =$ 271.8 Hz), δ_{C3} 123.5 ppm (m), δ_{C5} 126.7 ppm (m), δ_{C6} 127.6 ppm (s), $\delta_{C11,C13}$ 128.1 ppm (s), δ_{C12} 128.4 ppm (s), $\delta_{C10,C14}$ 129.0 ppm (s), δ_{C7} 129.9 ppm (t, $^3J_{C-F} =$ 5.7 Hz), δ_{C4} 130.4 ppm (q, $^2J_{C-F} = 32.4$ Hz), δ_{C2} 134.6 ppm (t, $^2J_{C-F} = 26.7$ Hz), δ_{C9} 135.4 ppm (t, $^3J_{C-F} = 2.9$ Hz); ^{19}F NMR: δ_{F15} −63.0 ppm (s), δ_{FA1} −105.7 ppm (dd, 1F, $^3J_{H-FA} = 8.9$ Hz, $^2J_{FA-FB} = 249.6$ Hz), δ_{FB1} −107.4 ppm (dd, 1F, $^3J_{H-FB} = 8.9$ Hz, $^2J_{FA-FB} = 249.6$ Hz); IR: 3382, 2977, 1958, 1908, 1813, 1738, 1694, 1622, 1495, 1454, 1337, 1247, 1170, 1131, 1079; MS: m/z (relative intensity): 302 (M^+, <1), 283 (7), 195 (11), 145 (5), 107 (100), 79 (58), 77 (34), 51 (10); high resolution MS: $M = 302.073006$ (302.071471, +5.1 ppm).

Acknowledgements

The financial support by Rhodia Recherche, Electricité de France, CNRS, Ministère EN and Région Aquitaine (France) is gratefully acknowledged.

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