SYNTHESIS OF 4-FLUOROPHENOLS FROM 4-*tert*-BUTYLPHENOLS AND FLUORIDE SOURCES UNDER OXIDATIVE CONDITIONS

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Dedicated to the memory of Professor Miloš Hudlický.

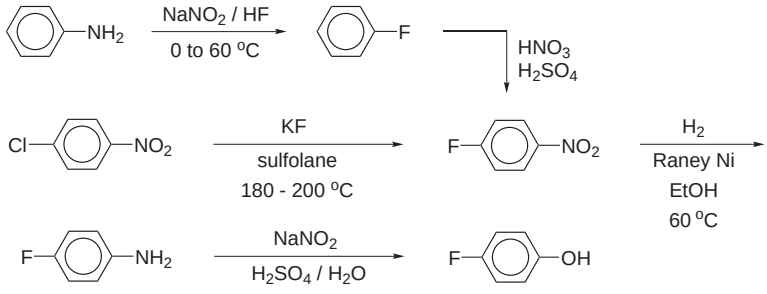
4-*tert*-Butylphenols can be easily transformed into 4-fluorophenols, provided that no coordinating moiety is present in 2-position, in a two step procedure under mild and safe conditions. The first step leads to 4-*tert*-butyl-4-fluorocyclohexa-2,5-dien-1-ones through an oxidative fluorination with [bis(trifluoroacetoxy)iodo]benzene and triethylamine tris(hydrofluoride), and is followed by an acid catalyzed aromatization with loss of isobutene. When extended to 4-*tert*-butylacetanilide, this method delivers 4-fluoroacetanilide in a single step but in a modest yield.

Keywords: Fluoroaromatics; Fluorinated compounds; 4-Fluorophenols; 4-*tert*-Butylphenols; 4-Fluoroacetanilide; 4-*tert*-Butylacetanilide; Oxidations; [Bis(trifluoroacetoxy)iodo]benzene; Triethylamine tris(hydrofluoride); Fluorinations.

4-Fluorophenol is the precursor of numerous biologically active compounds available on the industrial scale: Butofilolol, Nebivolol, Cisapride, Progabide, Sabeluzole, Sorbinil, Flumiclorac, Flumipropyn, Quinoxyphen, *etc.*[1] It can be prepared, as a mixture with its 2-isomer, by fluorination of phenol with fluorine at low temperature[2]. As this technique is difficult to scale up, diazotization of 4-fluoroaniline in aqueous sulfuric acid is routinely preferred[3]. The latter substrate arises from 1-fluoro-4-nitrobenzene, which is obtained either by nitration of fluorobenzene or by halogen exchange ("Halex" process) with alkaline fluorides from 4-chloronitrobenzene[2,3] (Scheme 1).

These two pathways to 4-fluorophenol suffer from several drawbacks. The first route from aniline needs two diazotization steps which are difficult to scale up and fluorine is introduced very early; moreover, nitration of

fluorobenzene is not totally *para*-regioselective (*para*/*ortho* = 91 : 9). In the second route, a high temperature is required for halogen exchange which is typically carried out in a high-boiling aprotic solvent the recycling of which could be troublesome.



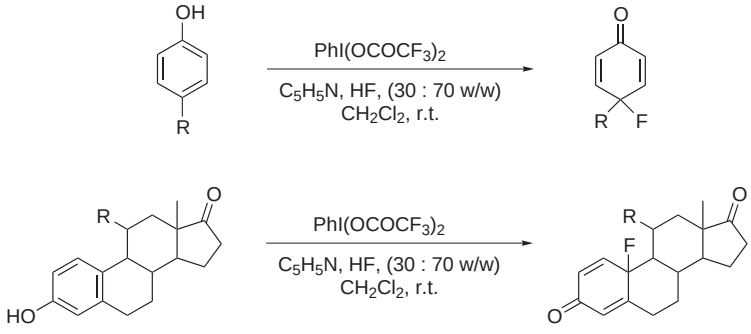
SCHEME 1

It must be noticed that, in contrast to other fluoroaromatics, 4-fluorophenol cannot be prepared by standard diazotization of 4-aminophenol in anhydrous hydrogen fluoride (Balz–Schiemann reaction) because of extensive formation of side-products[4].

An efficient modification has been proposed by Yoneda *et al.*, who used pyridinium poly(hydrogen fluoride) (Olah's reagent, Py/HF = 30 : 70 w/w) instead of hydrogen fluoride as solvent, but good yields of fluorophenol can be reached under very strictly controlled conditions only[5]. Thus, a more chemo- and regioselective access to 4-fluorophenol under mild conditions has to be found.

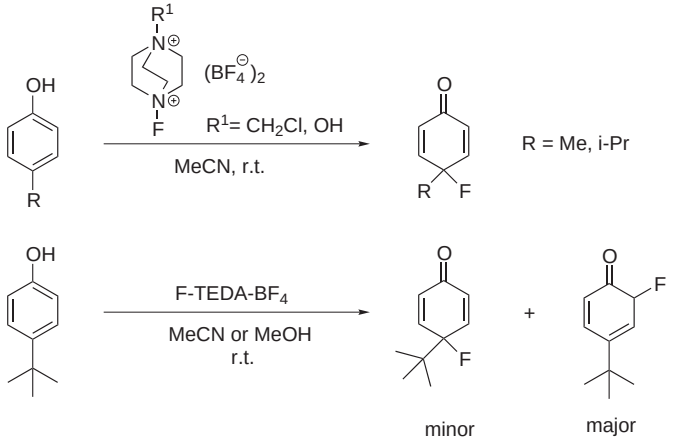
Some years ago, Jacquesy *et al.* described an interesting oxidative fluorination of 4-alkylphenols into 4-alkyl-4-fluorocyclohexa-2,5-dien-1-ones, using [bis(trifluoroacetoxy)iodo]benzene (also called phenyliodine bistrifluoroacetate, PIFA) as oxidizing agent and Olah's reagent as the fluoride source[6] (Scheme 2). Apart from the fact that the resulting product cannot be rearomatized into a fluorobenzene derivative, this reaction was carried out in an agressive medium which is not compatible with a glass apparatus. Moreover, in our hands this technique prove not to be suitable for the oxidative fluorination of 4-*tert*-butylphenol.

More recently, 4-alkyl-4-fluorocyclohexa-2,5-dien-1-ones were also obtained from 4-alkylphenols and 1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (Selectfluor™ or F-TEDA-BF4) or its 1-hydroxy analogue (Accufluor™), acting as oxidizers and fluorinating agents[7]. Good yields (> 80%) and complete regioselectivities were usually reached, except for 4-*tert*-butylphenol which led to two regioisomers



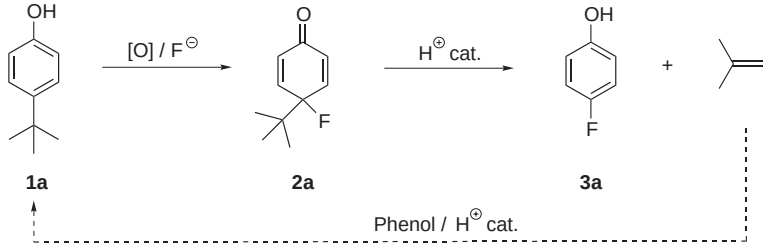
SCHEME 2

(Scheme 3). Such a process is more realistic than the previous oxidative fluorination of phenols with CF_3OF [8], ClO_3F [9], N-fluoro bis(perfluoroalkane)-sulfonimides[10], F_2 [11] or Pb(IV)/F^- sources (Olah's reagent, $Et_3N{\cdot}3HF$)[12]; nevertheless, it needs an expensive reagent which is not yet available on a large scale.



SCHEME 3

The comparative analysis of Jacquesy's and Stavber's works led us to proposal of a new two-step route to 4-fluorophenol (**3a**). Having in mind the easy protosubstitution of *tert*-butylated aromatics, 4-*tert*-butylphenol (**1a**) was chosen as starting material on which oxidative fluorination should be first applied. The formed 4-*tert*-butyl-4-fluorocyclohexa-2,5-dien-1-one (**2a**) should be then submitted to acid-catalyzed aromatization. In this second step, isobutene would be expelled and could be recycled for the preparation of 4-*tert*-butylphenol (Scheme 4).



SCHEME 4

For the first step, [bis(trifluoroacetoxy)iodo]benzene was chosen as oxidizer but instead of Olah's reagent, the handling of which is troublesome, other sources of more nucleophilic fluorides were tested. Preliminary results indicated that dichloromethane was the most appropriate solvent since the nucleophilic ones, such as dibutyl ether, sulfolane, or acetonitrile probably compete with fluoride. The results are listed in Table I.

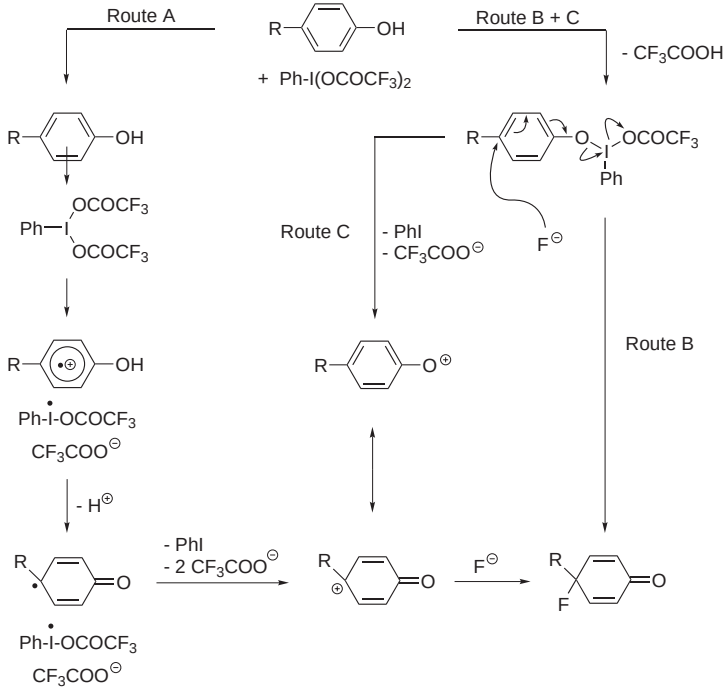
TABLE I
Oxidative fluorination of 4-*tert*-butylphenol with $PhI(OCOCF_3)_2$ and fluorides to 4-*tert*-butyl-4-fluorocyclohexa-2,5-dien-1-ones ($PhI(OCOCF_3)_2$, 1.3 eq., CH_2Cl_2, room temperature)

Entry	F^- Sources	No. of equivalents	Temperature °C	Isolated yield %
1	$Et_3N{\cdot}3HF$	1	25	10
2	$Et_3N{\cdot}3HF$	2	25	36
3	$Et_3N{\cdot}3HF$	3	25	62
4	$Et_3N{\cdot}3HF$	3	0	62
5	$Et_3N{\cdot}3HF$[a]	3	25	40
6	$Et_3N{\cdot}2HF$[b]	3	25	46
7	KHF_2	3	25	(27)[c]
8	KF/18-crown-6	3	25	22
9	KF/cryptand[2.2.2]	3	25	0
10	$Me_4NF{\cdot}4H_2O$	3	25	3
11	anhydrous Me_4NF	3	25	3

[a] In CH_2Cl_2/H_2O (50 : 1 v/v), *p*-benzoquinone observed as by-product. [b] Formed *in situ* from $Et_3N{\cdot}3HF$ and Et_3N (1 : 1). [c] Crude yield from ^{19}F NMR with $PhOCF_3$ as internal standard.

Table I clearly shows that the $Et_3N{\cdot}3HF$ complex (equivalent to $Et_3NH^+H_2F_3^-$) behaves as the best fluoride source, provided that 3 equivalents are used, either at room temperature (entry 3) or at 0 °C (entry 4). Interestingly, this solvated fluoride is advantageous over Olah's reagent because it is more stable, less hygroscopic and more nucleophilic, it does not emit any HF fumes (even under heating or distillation), it is not acidic and can be used in glassware. It can be noticed that comparative yields were obtained from $Et_3N{\cdot}3HF$ and 4-*tert*-butylphenol (62%) on one hand, and from Olah's reagent and 4-ethylphenol (61%) or 4-methylphenol (68%)[6a] on the other hand. In the latter case, electrophilic dimerization of the substrate occurred as a side-reaction[6a]. Because of the bulkiness of the *tert*-butyl group, such a dimerization was not observed for 4-*tert*-butylphenol. However, other nucleophilic species, such as water (entry 5) or ethers (*e.g.* crown ethers, entry 8) interfere with fluoride anion and must be avoided, as well as oxidizable compounds such as triethylamine (entry 6) or cryptand [2.2.2] (entry 9).

Such a sensitivity to competing nucleophiles strongly suggests that intermediate cationic species were formed. Several mechanisms, reported in Scheme 5, can be considered: either two consecutive single-electron trans-



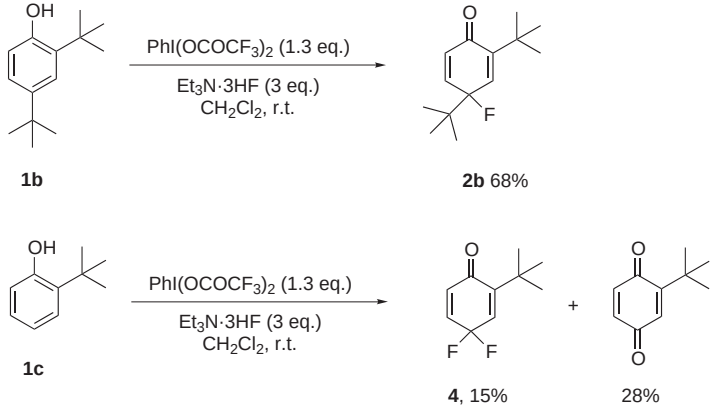
SCHEME 5

fers leading first to a radical-cation then to a cation, as suggested by Eberson *et al.*[13] and Kita *et al.*[14] (route A), or formation of a cationic complex from iodine(III) which could be transformed in a concerted way (route B) or deliver a phenoxylenium cation (route C)[15,16].

As the replacement of PIFA by several other oxidizers (ceric ammonium nitrate (CAN), $CuCl/Fe(NO_3)_3/H_2O_2$, CuCl/*t*-BuOOH, CuCl/*t*-BuOOH/$Fe(NO_3)_3$, $FeCl_3$, $K_2S_2O_8/(NH_4)_2FeSO_4$), known to oxidize phenols through a single-electron transfer, failed in our hands to afford dienone **2a** from phenol **1a** and $Et_3N{\cdot}3HF$, it can be suggested that route A was not involved in the oxidative fluorination. Our experiments did not allow any choice between route B and route C but strong evidences have been recently brought in favour of route C [15,16].

Concerning the replacement of PIFA by another oxidizer, it must be also mentioned that the use of lead tetraacetate was disappointing: dienone **2a** was obtained in a 7% yield only.

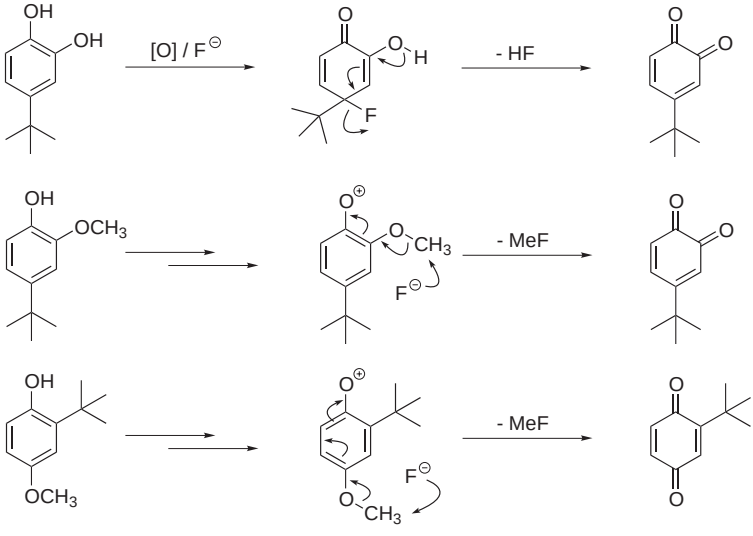
Oxidative fluorination with PIFA and $Et_3N{\cdot}3HF$ was then applied to 2,4-di-*tert*-butylphenol (**1b**) and 2-*tert*-butylphenol (**1c**) (Scheme 6). The expected compound **2b** was obtained in a satisfactory yield from phenol **1b** as a single regioisomer; indeed, fluorination occurred exclusively at the *para*-position, probably because of steric factors. Surprisingly, phenol **1c** was also fluorinated at the 4-position instead of the expected 2-position, on which a cationic charge should have been stabilized. Moreover, as the monofluorinated intermediate can be aromatized, oxidative fluorination occurred twice. The resulting 2-*tert*-butyl-4,4-difluoro-2,5-cyclohexadien-1-one (**4**), which bears water-sensitive allylic fluorine atoms, was contaminated with *tert*-butyl-*p*-benzoquinone after work-up. In the same way,



SCHEME 6

3-*tert*-butylphenol afforded 3-*tert*-butyl-4,4-difluoro-2,5-cyclohexadien-1-one only in a 8% yield, along with *tert*-butyl-*p*-benzoquinone again.

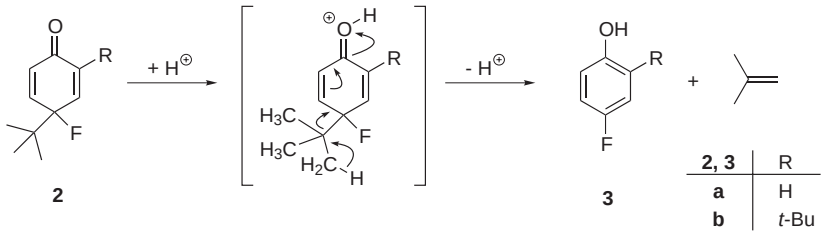
4-*tert*-Butylbenzene-1,2-diol, 4-*tert*-butyl-2-methoxyphenol and 2-*tert*-butyl-4-methoxyphenol failed to afford fluorinated products but *tert*-butylbenzoquinones were formed in all cases, probably along with some polymeric materials (Scheme 7). In fact, oxidative fluorination probably occured on 4-*tert*-butylbenzene-1,2-diol but the fluorinated intermediate obviously lost hydrogen fluoride. The transformation of the two other substrates could bring arguments for the occurence of phenoxylenium cations, as already proposed[15,16].



SCHEME 7

To obtain the target 4-fluorophenols **3** through the rearrangement described in Scheme 8, 4-*tert*-butyl-4-fluorocyclohexa-2,5-dien-1-ones **2a** and **2b** were subjected to an acidic treatment, either with trifluoroacetic acid or with solution of anhydrous hydrogen chloride in diethyl ether. These two acidic media were used as solvents. The results are reported in Table II.

From these data, it appears that 4-fluorocyclohexa-2,5-dien-1-ones **2a** and **2b** can yield the corresponding 4-fluorophenols **3a** and **3b** in trifluoroacetic acid at room temperature (entries 1 and 5); the yields were satisfactory but the reactions were slow (one day). Heating to reflux increased dramatically the rate but decreased the yield because of growing role of side reactions (entry 2).



SCHEME 8

In contrast, no aromatization occurred in $HCl \cdot Et_2O$ at room temperature and reflux was needed to obtain fluorophenols **3** in this medium. Consequently, the reaction had to be carried out in a sealed vessel to prevent HCl loss. HCl concentration was also a crucial parameter: with a 0.71 M solution, the reaction was slow and 4-fluorophenol (**3a**) formed along with its *tert*-butyl ether (entry 3), whereas with a 2.0 M solution, the reaction was complete in 8 h, the yield was not affected and 4-fluorophenols **3** were obtained as the sole products (entries 4 and 6).

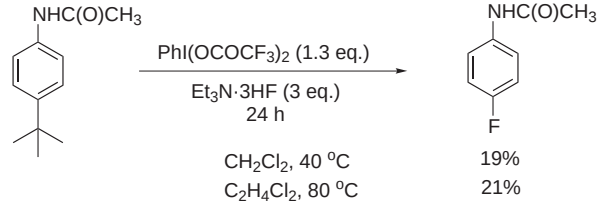
Like 4-fluorophenol (**3a**), 4-fluoroaniline is an important building block for the preparation of biologically active compounds. Thus, we decided to extend our successful two-step synthesis of 4-fluorophenol (**3a**) to the preparation of 4-fluoroaniline from 4-*tert*-butylaniline. 4-*tert*-Butylaniline itself was, however, too oxidizable to react cleanly and was probably protonated

TABLE II
Aromatization of 4-*tert*-butyl-4-fluorocyclohexa-2,5-dien-1-ones **2a** and **2b**

Entry	Substrate	Acid	Eq. H^+	Time h	Temperature °C	Isolated yield %
1	**2a**	CF_3CO_2H	5	24	25	**3a** 57
2	**2a**	CF_3CO_2H	10	1	72 (reflux)	**3a** 48
3	**2a**	HCl/Et_2O (0.71 M)[a]	5	71	40	**3a** 62[b]
4	**2a**	HCl/Et_2O (2.0 M)[a]	5	7	40	**3a** 57
5	**2b**	CF_3CO_2H	2	22	25	**3b** 52
6	**2b**	HCl/Et_2O (2.0 M)[a]	5	8	40	**3b** 61

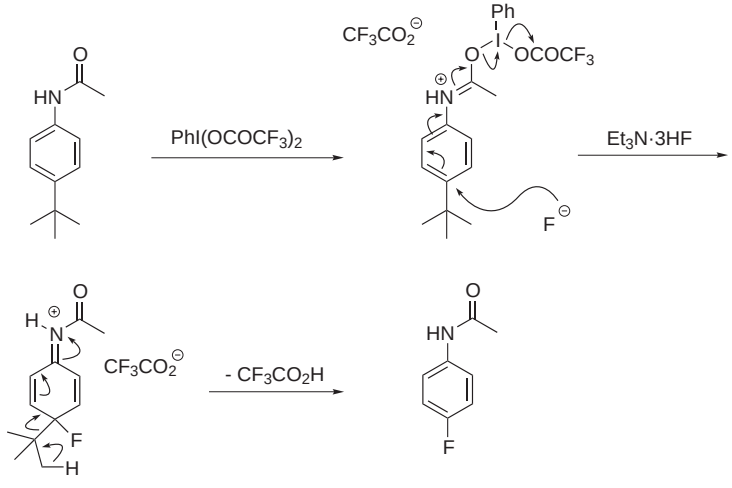
[a] Carried out in a sealed vessel; [b] *p*-FC_6H_4OH (35%) + *p*-FC_6H_4O-*t*-Bu (27%).

during reaction with PIFA. Consequently, no fluorinated product was formed, either at room temperature or upon heating. So, 4-*tert*-butylacetanilide was chosen as another starting material. No reaction occurred at room temperature among this substrate, PIFA and $Et_3N{\cdot}3HF$ in dichloromethane but, at reflux for one day, 4-fluoroacetanilide was directly obtained, though in a modest yield, instead of the expected 4-*tert*-butyl-4-fluorocyclohexa-2,5-dien-1-imine. The yield was slightly improved when the reaction was carried out in 1,2-dichloroethane at reflux (Scheme 9).



SCHEME 9

The difference in reactivity between 4-*tert*-butylphenol and 4-*tert*-butylacetanilide could be explained by the lower nucleophilicity of the latter substrate towards iodine(III) on one hand, and the fact that the nitrogen equivalent of a phenoxylium ion could be not formed on the other hand. Indeed, the reaction mechanism could be modified when moving from oxygen to nitrogen, for example in such a way that the nitrogen atom could be protonated throughout all process, a fact which could explain the direct formation of fluoroaniline (Scheme 10).



SCHEME 10

In conclusion, 4-*tert*-butylphenols **1** can be easily transformed into 4-fluorophenols **3**, provided that no coordinating moiety is present in the 2-position, in a two step procedure under mild and safe conditions. The first step leads to 4-*tert*-butyl-4-fluorocyclohexa-2,5-dien-1-ones **2** through oxidative fluorination with [bis(trifluoroacetoxy)iodo]benzene and triethylamine tris(hydrofluoride), and is followed by an acid catalyzed aromatization with loss of isobutene. When extended to 4-*tert*-butylacetanilide, this method affords 4-fluoroacetanilide in a single step, avoiding the aromatization step, but, so far, the yield is modest and work is in progress to improve this result.

Finally, this two-step synthesis of fluorophenols corresponds formally to electrophilic fluorination of phenols and anilines.

EXPERIMENTAL

Prior to use, solvents were stored over 3 Å molecular sieves under nitrogen, KF and KHF_2 were dried by azeotropic distillation of their suspensions in toluene, and 4-*tert*-butylphenol, as well as 2,4-di-*tert*-butylphenol were purified by sublimation. Other reagents were used as received. 4-*tert*-Butylacetanilide was prepared by acetylation of 4-*tert*-butylaniline with acetic anhydride. TLC analyses were carried out on Kieselgel 60F 254 deposited on aluminium plates, detection being done by UV (254 nm). Flash chromatography was performed on silica gel Geduran SI 60 (230–400 mesh). Uncorrected melting points were determined in capillary tubes. Unless stated otherwise, NMR spectra were recorded in $CDCl_3$. ^1H NMR spectra were recorded at 200 or 300 MHz and ^{13}C NMR spectra at 50 or 75 MHz. Substitution patterns of different carbons were determined by a DEPT 135 sequence. ^{19}F NMR spectra were recorded at 188 MHz. Chemical shifts (δ) are given in ppm *vs* TMS (^1H, ^{13}C) or $CFCl_3$ (^{19}F) used as internal references. Coupling constants (*J*) are given in Hz. Crude yields were determined by ^{19}F NMR *vs* $PhOCF_3$ used as internal standard. GC was carried out on an apparatus fitted with a semi capillary column (length 15 m, i.d. 0.53 mm, film thickness (DB1) 1 μm) and a catharometric detector. Mass spectrometry, coupled with gas chromatography, was carrried out under electron impact at 70 eV.

Oxidative Fluorination of 4-*tert*-Butylphenol (**1a**) and 2,4-Di-*tert*-butylphenol (**1b**). General Procedure

A flame-dried three-necked vessel was successively charged, under nitrogen, with the phenol **1a** or **1b** (4 mmol), dichloromethane (50 ml) and the fluoride source (3 eq.). The resulting mixture was stirred at room temperature for 30 min, then cooled to 0 °C with an ice bath before dropwise addition, within 1 h, of [bis(trifluoroacetoxy)iodo]benzene (1.3 eq.), dissolved in dichloromethane (30 ml). The reaction medium was warmed to room temperature and kept under stirring for 24 h. Then, it was washed with a 12.5% aqueous solution of ammonia until neutral and decanted. The organic phase was dried over $MgSO_4$ and evaporated *in vacuo*. The crude residue was separated and purified by column chromatography. Iodobenzene was first eluted with pure petroleum ether, then dienones **2a** or **2b** were eluted with a petroleum ether/ethyl acetate mixture (80 : 20).

4-tert-Butyl-4-fluorocyclohexa-2,5-dien-1-one (**2a**). Reaction according to general procedure afforded dienone **2a** as a brown solid (62%, 410 mg). ^{1}H NMR (200 MHz, $CDCl_3$): 7.00 (dd, 2 H, $^3J_{HH}$ = 10.1 and $^3J_{HF}$ = 7.0, H-3, H-5); 6.28 (d, 2 H, $^3J_{HH}$ = 10.1, H-2, H-6); 1.06 (s, 9 H, *t*-Bu). ^{13}C NMR (75 MHz, $CDCl_3$): 184.69 (C=O); 145.06 (d, $^2J_{CF}$ = 22.6, C-3, C-5); 130.04 (C-2, C-6); 92.92 (d, $^1J_{CF}$ = 169, C-4); 38.98 (d, $^2J_{CF}$ = 23.2, $C(CH_3)_3$); 25.15 (d, $^3J_{CF}$ = 3.4, CH_3). ^{19}F NMR (188 MHz, $CDCl_3$): –162.54 (t, $^3J_{FH}$ = 7.0). MS, *m/z*: 112 ($M^{\bullet+}$ – C_4H_8), 83, 63, 57, 55.

2,4-Di-tert-butyl-4-fluorocyclohexa-2,5-dien-1-one (**2b**). Reaction according to general procedure afforded dienone **2b** as a deep green solid (68%, 616 mg). ^{1}H NMR (300 MHz, $CDCl_3$): 6.87 (ddd, 1 H, $^3J_{HH}$ = 10.4, $^3J_{HF}$ =7.4, $^4J_{HH}$ = 3.1, H-5); 6.74 (dd, 1 H, $^3J_{HF}$ = 8.6, $^4J_{HH}$ = 3.1, H-3); 6.18 (d, 1 H, $^3J_{HH}$ = 10.4, H-6); 1.24 (s, 9 H, 2-*t*-Bu); 1.10 (d, 9 H, $^4J_{HF}$ = 1.1, 4-*t*-Bu). ^{13}C NMR (75 MHz, $CDCl_3$): 184.88 (C=O); 147.46 (d, $^3J_{CF}$ = 9.0, C-2); 142.79 (d, $^2J_{CF}$ = 22.6, C-3 or C-5); 138.69 (d, $^3J_{CF}$ = 23.7, C-3 or C-5); 131.70 (d, $^3J_{CF}$ = 9.0, C-6); 94.10 (d, $^1J_{CF}$ = 168, C-4); 39.35 (d, $^2J_{CF}$ = 23.7, 4-$C(CH_3)_3$); 34.83 (d, $^4J_{CF}$ = 1.1, 2-$C(CH_3)_3$); 29.11 (2-C$(CH_3)_3$); 25.32 (d, $^3J_{CF}$ = 3.9, 4-C$(CH_3)_3$). ^{19}F NMR (188 MHz, $CDCl_3$): –162.62.

2-tert-Butyl-4,4-difluorocyclohexa-2,5-dien-1-one (**4**). The same procedure was applied except that, after the end of the reaction, the medium was stirred with solid K_2CO_3 (2 to 3 g) for 1 h, then filtered and dichloromethane was evaporated *in vacuo*. The crude residue was purified by column chromatography in the same way as for dienones **2a** and **2b**. *tert*-Butyl-*p*-benzoquinone was thus separated to afford dienone **4** as yellow solid (15%, 112 mg). ^{1}H NMR (300 MHz, $CDCl_3$): 6.72 (ddt, 1 H, $^3J_{HH}$ = 10.0, $^3J_{HF}$ = 6.3, $^4J_{HH}$ = 3.4, H-5); 6.56 (dt, 1 H, $^3J_{HF}$ = 6.3, $^4J_{HH}$ = 3.4, H-3); 6.22 (d, 1 H, $^3J_{HH}$ = 10.0, H-6); 1.25 (s, 9 H, *t*-Bu). ^{13}C NMR (75 MHz, $CDCl_3$): 184.23 (C=O); 149.52 (C-2); 135.34 (t, $^2J_{CF}$ = 28.3, C-3 or C-5); 133.24 (t, $^3J_{CF}$ = 9.4, C-6); 131.49 (t, $^2J_{CF}$ = 28.3, C-3 or C-5); 111.32 (t, $^1J_{CF}$ = 207.0, C-4); 34.81 (s, $C(CH_3)_3$); 28.90 (s, CH_3). ^{19}F NMR (188 MHz, $CDCl_3$): –97.8. MS, *m/z*: 186 ($M^{\bullet+}$), 171, 151, 144, 143, 139, 109, 107, 103, 83, 77, 76, 75, 67, 65, 39, 29, 27.

Acid Catalyzed Aromatization of Dienones **2a** and **2b**.
General procedure

Cyclohexadienone **2a** or **2b** (1 mmol) was placed in a one-necked vessel with trifluoroacetic acid (5 eq.) or a 2 M solution of hydrogen chloride in Et_2O. After sealing the vessel, the mixture was stirred at room temperature for 24 h (CF_3COOH) or at reflux for 8 h (HCl, Et_2O). Then, the acid was evaporated *in vacuo* and the crude residue was purified by column chromatography with petroleum ether/ethyl acetate (90 : 10) as eluent.

4-Fluorophenol (**3a**). Reaction according to general procedure afforded phenol **3a** as a white solid (57%, 64 mg). M.p. 46 °C (commercial sample: 48 °C).

2-tert-Butyl-4-fluoro-phenol (**3b**). Reaction according to general procedure afforded phenol **3b** as a pale brown liquid (61%, 106 mg). ^{1}H NMR (300 MHz, $CDCl_3$): 6.98 (dd, 1 H, $^3J_{HF}$ = 10.5, $^4J_{HH}$ = 3.1, H-3); 6.74 (ddd, 1 H, $^3J_{HH}$ = 8.5, $^3J_{HF}$ = 7.4, $^4J_{HH}$ = 3.1, H-5); 6.61 (dd, 1 H, $^3J_{HH}$ = 8.5, $^4J_{HF}$ = 5.3, H-2); 5.27 (s, 1 H, OH); 1.42 (s, 9 H, *t*-Bu). ^{13}C NMR (50 MHz, $CDCl_3$): 156.88 (d, $^1J_{CF}$ = 236, C-4); 150.68 (d, $^4J_{CF}$ = 2.1, C-1); 138.15 (d, $^3J_{CF}$ = 6.0, C-2); 116.83 (d, $^3J_{CF}$ = 8.2, C-6); 113.90 (d, $^2J_{CF}$ = 23.8, C-3 or C-5); 112.50 (d, $^2J_{CF}$ = 22.8, C-3 or C-5); 34.78 (s, $C(CH_3)_3$); 29.30 (s, CH_3). ^{19}F NMR (188 MHz, $CDCl_3$): –124.56 (s). MS, *m/z*: 168($M^{\bullet+}$), 153, 149, 133, 125, 109, 57.

4-Fluoroacetanilide

A flame-dried three-necked vessel was successively charged, under nitrogen, with 4-*tert*-butylacetanilide (765 mg, 4 mmol), dichloromethane (50 ml) and $Et_3N{\cdot}3HF$ (1.95 ml, 3 eq.). The resulting mixture was stirred at room temperature for 30 min and then [bis(trifluoroacetoxy)iodo]benzene (2.24 g, 1.3 eq.), dissolved in dichloromethane (30 ml), was dropwise added. The reaction mixture was then kept under reflux for 24 h, washed with a 12.5% aqueous solution of ammonia until neutral and decanted. The organic phase was dried over $MgSO_4$ and evaporated *in vacuo* to afford a yellow solid (19%, 29 mg). M.p. 150 °C. ^{1}H NMR (300 MHz, $CDCl_3$): 7.43 (m, 2 H, H-2 and H-6); 6.99 (m, 2 H, H-3 and H-5); 2.16 (s, 3 H, CH_3). ^{19}F NMR (282 MHz, $CDCl_3$): –118.43 (m). (These spectral features were in complete accordance with those of an authentic sample of 4-fluoroacetanilide, prepared from commercial 4-fluoroaniline and acetic anhydride).

REFERENCES

1. Becker A.: *Inventory of Industrial Fluoro-Biochemicals*. Eyrolles, Paris 1996.
2. Clark J. H., Wails D., Bastock T. W.: *Aromatic Fluorination*. CRC, Boca Raton 1996.
3. a) Banks R. E., Smart B. E., Tatlow J. C.: *Organofluorine Chemistry: Principles and Commercial Applications*. Plenum Press, New York 1994; b) Hudlický M., Pavlath A.: *Chemistry of Organic Fluorine Compounds II. A Critical Review*. American Chemical Society, Washington D. C. 1995.
4. Langlois B. R. in: *Houben Weyl Methods of Organic Chemistry* (B. Baasner, H. Hagemann and J. C. Tatlow, Eds), 4th ed., Vol. E10a, p. 686. Georg Thieme, Stuttgart 1999.
5. a) Yoneda N.: *Tetrahedron* **1991**, *47*, 5329; b) Fukuhara T., Yoneda N., Takamura K., Suzuki A.: *J. Fluorine Chem.* **1991**, *51*, 299.
6. a) Karam O., Jacquesy J. C., Jouannetaud M. P.: *Tetrahedron Lett.* **1994**, *35*, 2541; b) Martin A., Jouannetaud M. P., Jacquesy J. C., Cousson A.: *Tetrahedron Lett.* **1996**, *37*, 7735; c) Karam O., Martin A., Jouannetaud M. P., Jacquesy J. C.: *Tetrahedron Lett.* **1999**, *40*, 4183.
7. Stavber S., Jereb M., Zupan M.: *Synlett* **1999**, *9*, 1375.
8. Barton D. H. R., Hesse R. H., Pechet M. M., Toh H. T.: *J. Chem. Soc., Perkin Trans. 1* **1974**, 732.
9. Mills J. S., Barrera J., Olivares E., Garcia H.: *J. Am. Chem. Soc.* **1960**, *82*, 5882.
10. a) Pennington W. T., Resnati G., DesMarteau D. D.: *J. Org. Chem.* **1992**, *57*, 1536; b) Singh S., DesMarteau D. D., Zuberi S. S., Witz M., Huang H. N.: *J. Am. Chem. Soc.* **1987**, *109*, 7194.
11. Misaki S.: *J. Fluorine Chem.* **1981**, *17*, 159.
12. Meurs J. H. H., Sopher D. W., Eilenberg W.: *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 927.
13. Eberson L., Hartshorn M. P., Persson O., Radner F.: *Chem. Commun.* **1996**, 2105.
14. Kita Y., Tohma H., Inagaki M., Hatanaka K., Yakura T.: *Tetrahedron Lett.* **1991**, *32*, 4321.
15. Kürti L., Herczegh P., Visy J., Simonyi M., Antus S., Pelter A.: *J. Chem. Soc., Perkin Trans. 1* **1999**, 379.
16. Pelter A., Ward R. S.: *Tetrahedron* **2001**, *57*, 273.