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Fluorination of aromatic compounds from 1-aryl-3,3-dimethyltriazenes and fluoride anions in acidic medium 1. A model for ^{18}F labelling

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Abstract

Decomposition of 1-aryl-3,3-dialkyltriazenes by strong and non-nucleophilic acids (CF_3SO_3H, H_2SO_4) can be achieved at 90°C in carbon tetrachloride, in the presence of sub-stoichiometric amounts of fluoride anions. Yields of fluoroarenes up to 39% (versus F^-) can be reached under these conditions, within 15–30 min and without contamination of the fluorinated compounds by inseparable by-products. Such conditions and results enable an adaptation to radiofluorination with $^{18}F^-$. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Fluorination; Triazene; Fluoride; Fluorine 18

1. Introduction

Positron emission tomography (PET) is now routinely used for the medical imaging of the human body because of the short half-life and huge specific radioactivity of positron emitters which allow repetitive administration of very low radiation doses [1]. ^{18}F is one of the most popular β^+-labelling isotope because its rather long half-time ($t_{1/2} = 110$ min) is compatible with the preparation of sophisticated [^{18}F]-labelled drugs and the study of slow biological processes [2,3]. For example, (*S*)-6-[^{18}F]fluoro-DOPA is routinely used, as well as its α-methyl derivative [5], to study neurotransmission disorders such as epilepsy [1], Alzheimer's disease [1] or Parkinson's disease [4]. It also constitutes a potent tool for pharmacological studies in vivo [6]. Other aromatic aminoacids (or derivatives) and neuroleptics have been also described [2].

Usually, the preparation of β^+-radiolabelled tracers must be arranged in such a way that the short-lived radioisotope is introduced in the later stages of the synthetic chain in order to get the best specific radioactivity. Unfortunately, until now, the synthesis of [^{18}F]fluoroaromatic aminoacids does not respect this criterion since fluorine is usually introduced in the early stages by a nucleophilic substitution with $^{18}F^-$ fluoride anion, which is the most available source of ^{18}F. In our opinion, this problem could be circumvented by lately introducing fluorine on aromatic nuclei through the acidic decomposition of 1-aryl-3,3-dialkyltriazenes in the presence of fluoride anions. The advantage of this technique would rest on the properties of the triazeno moiety, a stable equivalent of a diazo group [7], which could be introduced in the early stages of the synthetic chain. Then, the triazenated product could be isolated, purified and functionalized, provided that the following reactions are performed under non-acidic conditions [8]. So, the fluorodetriazenation step could be carried on sophisticated triazenes, in the latest stages of the synthesis. To verify the key-step of our strategy, we examine, in this paper, the transformation of simple aryltriazenes into fluoroaromatics with fluorides.

2. Results and discussion

1-Aryl-3,3-dialkyltriazenes are readily obtained from arenediazonium chlorides and secondary amines [9–11]. They can be easily isolated and purified. Their transformation into fluoroarenes by a large excess of hydrogen fluoride has been recently reviewed [10]. This technique has been adapted to ^{18}F incorporation by using limited amounts of $H^{18}F$ in protic solvents [12,13]. But, as $H^{18}F$ is not easily available, it has been replaced by $Cs^{18}F$ (in deficiency) and an auxiliary acid (i.e. CH_3SO_3H used in excess), the reaction being carried out in an aprotic solvent [14]. Nevertheless, the results are dramatically dependent on the nature of the auxiliary acid and that of the solvent [15,16]. Especially,

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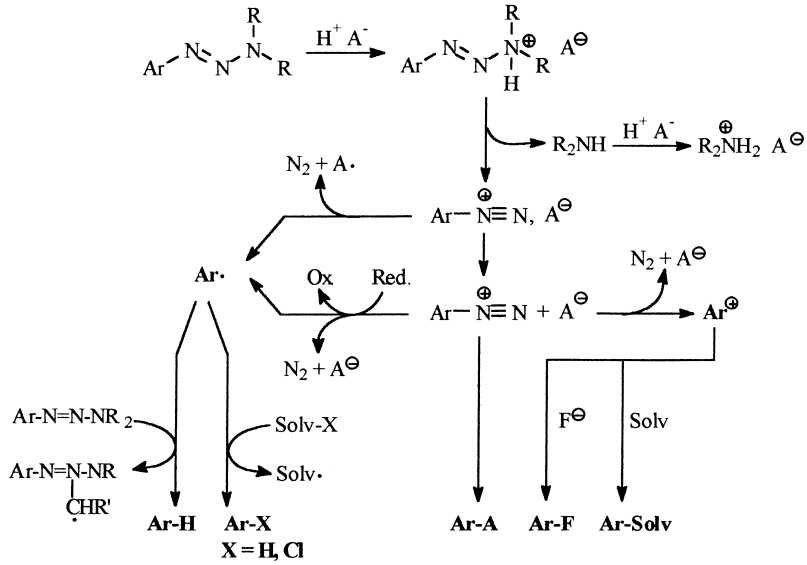


Scheme 1. Competitive processes during fluorodediazoniation.

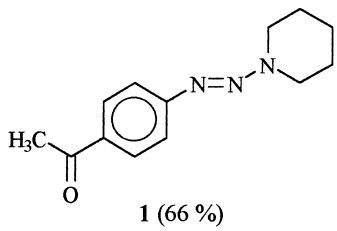
in hydrogen-containing solvents, large amounts of ArH are produced through radical hydrodetriazenation along with $Ar^{18}F$ (formed by ionic fluorodetriazenation). This constitutes a severe limitation since these two compounds are very difficult to separate, especially on the nanomole scale where radiofluorination must be carried out. Thus, we reinvestigated the acidic decomposition of aryltriazenes in the presence of non-radioactive fluoride anions ($^{19}F^-$), in order to rationalise the medium effects and find conditions which could be realistically transposed to radiofluorination.

During fluorodediazoniation in hydrogen- or chloro-containing solvents, several reactions can be considered (Scheme 1).

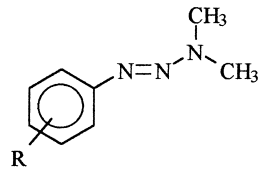
To build a good model for radiofluorination, the parameters must be consequently chosen in order that the radical processes, which produce ArH, can be suppressed and the ionic processes maximised, even if heavier products (Ar–Cl, Ar–A, Ar–Solv) are formed, since they can be easily separated from Ar–F. For example, solvents such as DMSO, HMPA, methanol or pyridine, which are known to reduce arenediazonium cations [17–23], must be avoided. We also preferred caesium fluoride, which can be efficiently dried, to more soluble but hygroscopic tetraalkylammonium fluorides, to avoid phenol formation. Finally, triflic and sulfuric acids were chosen as auxiliary acids because their conjugated bases have a sufficiently low nucleophilicity to minimise the formation of Ar–A.

The influence of the different parameters have been studied with simple 1-aryl-3,3-dialkyltriazenes (**1–5**) (Scheme 2) prepared according to Wallach [9], either in the presence of a base (**3–5**) or not (**1–2**). They were reacted, in a closed Teflon PFA® vessel, with dry CsF in the presence of a solvent and an acid. Several experiments were done with an excess of CsF (to be compared to already reported results) but, to be consistent with radiofluorination, others were carried out with a deficiency of CsF (in this case, fluoroaromatic yields are given versus CsF).

The first experiments, carried out with **1** ($C = 0.11\ mol^{-1}$), showed that the ratio between the liquid and the gas volumes in the closed vessel affected the ratio between ionic and radical processes. When the liquid volume increased, that means when the partial pressure of nitrogen in the gas phase increased, the ionic processes decreased. This observation is consistent with a postulated

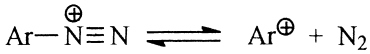


1 (66 %)



2 R = 4-MeC(O) (90 %)
3 R = 4-CH_3 (90 %)
4 R = 3-CH_3 (90 %)
5 R = 2-CH_3 (27 %)

Scheme 2. Starting aryltriazenes (yields of isolated compounds).



Scheme 3. Equilibrium between ArN_2^+, Ar^+ and N_2.

equilibrium between ArN_2^+, Ar^+ and N_2 (Scheme 3) [20,24], the better reducibility of ArN_2^+ (versus Ar^+) [17] and the fact that most ionic reactions arise from Ar^+. Consequently, all the further reactions were performed with a constant ratio between liquid and gas volumes ($V_l/V_g = 0.3$).

Then, reaction temperature and duration were examined. As for arenediazonium fluorides [10], the temperature required to significantly transform aryltriazenes is mainly dependent on the nature of the substrate. A 0.11 M solution of the less reactive starting material **1** must be heated up to 90°C for 1 h to be completely converted by triflic acid and caesium fluoride. Consequently, this temperature was adopted for the further experiments all the more so since we observed that the ratio between ionic processes (Ar–F + Ar–A + Ar–Solv) and radical processes (Ar–H) increased when raising the temperature (Table 1). Table 1 also shows that ArF/ArH increased with the reaction time. In other words, radical processes are both thermodynamically and kinetically favoured. It can be noticed (especially from **3**) that the maximum yield of ArF can be reached within 15–30 min, a duration that is compatible with radiofluorination.

As the introduction order of the reaction components, before heating, could be also important, three procedures were compared.

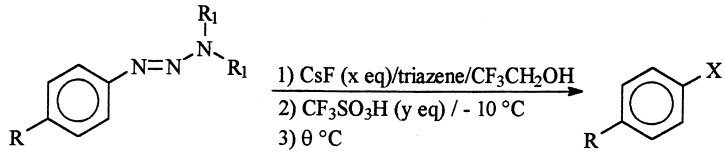
- Procedure A: (1) CsF + solvent; (2) acid (AH) at −10°C; (3) triazene at −10°C.
- Procedure B: (1) triazene + solvent; (2) acid (AH) at −10°C; (3) CsF at −10°C.
- Procedure C: (1) CsF + triazene + solvent; (2) acid (AH) at −10°C.

Procedure A led to the formation of HF in situ before addition of the triazene. When CsF was more abundant than AH, the triazene was protonated by a mixture of HF and $Cs^+ HF_2^-$. When CsF was less abundant than AH, the triazene was protonated by HF along with AH. Procedure B led first to the formation of $ArN_2^+ A^-$ which, then, was mainly decomposed by F^- (A^- was presumed to be less nucleophilic) and, eventually, the solvent. Procedure C constituted an intermediate case in which AH could competitively protonate F^- and the triazene. When an excess of CsF (versus triazene) was used, the comparative results in carbon tetrachloride and trifluoroethanol are summarised in Table 2.

In carbon tetrachloride (entries 1–3), fluoroarene formation was only slightly affected by the order of introduction of the reagents, though a little higher yield was observed with procedure A. In such a non-polar and viscous medium, all the reactive species, except triazene, are almost insoluble and interfacial processes are important. Reactions in solvent cages are also favoured. This phenomenon could explain why procedure A, in which $ArN_2^+ F^-$ is first formed in a solvent cage from triazene and HF/HF_2^-, delivered a better yield of ArF. In contrast, procedure B, in which $ArN_2^+ TfO^-$ was first formed in a solvent cage, favoured the formation of ArOTf, despite the low nucleophilicity of TfO^-.

It must be also noticed that procedure B was the only one which prevented radical process to occur (entry 2) whereas ArCl and ArH were formed from procedures A and C (entries 1 and 3). The occurrence of the latter, in a medium which did not contain any evident reducer or hydrogen atom donor, was surprising. To explain rather similar experiments, Satyamurphy et al. [16] postulated that an intramolecular single electron transfer could occur, from the anions to

Table 1
Influence of the reaction temperature and time



C = 0.11 Mol.L^{-1}

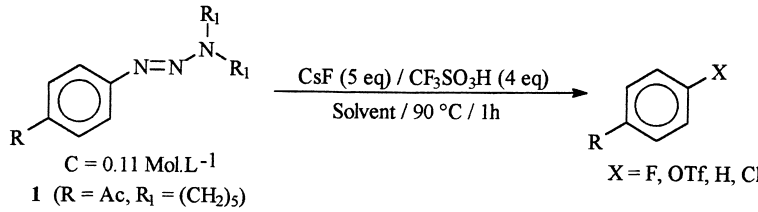
1 (R = Ac, R_1 = $(CH_2)_5$)

3 (R = Me, R_1 = Me)

Substrate; CsF (*x* eq); TfOH (*y* eq)	θ°C	Time (min)	Ar–F[a](%)	Ar–OTf[a,b](%)	Ar–H[a](%)	ArH/ArF
1; CsF (5 eq); TfOH (4 eq)	45	60	13	7	4	0.31
	80	60	24	11	Trace	ε
	90	60	26	12	0	0
3; CsF (0.2 eq); TfOH: (2.1 eq)	90	60	26	12	0	0
	90	30	25	7	1	0.04
	90	15	24	7	1	0.04
	90	9	16	7	2	0.13

[a] The major product $ArOCH_2CF_3$ (from incorporation of the solvent) was not determined.

Table 2
Influence of the introduction of the reaction components (CsF in excess)



Entry	Solvent	Procedure (see text)	ArF (%)	ArOTf (%)	ArH (%)	ArCl (%)
1	CCl_4	A	23	8	4	3
2		B	20	48	0	0
3		C	20	40	5	4
4	CF_3CH_2OH[a]	A	24	13	4	–
5		C	26	12	0	–

[a] The major product $ArOCH_2CF_3$ (from incorporation of the solvent) was not determined.

ArN_2^+, in arenediazonium trifluoroacetates and methanesulfonates. This internal redox process can be ruled out for arenediazonium triflates first because of the very low oxidability of the triflate anion and secondly because no ArH or ArCl appeared in procedure B where ArN_2^+ TfO^- was initially formed. So, we suspected that the non-protonated triazene could be the hydrogen donor.

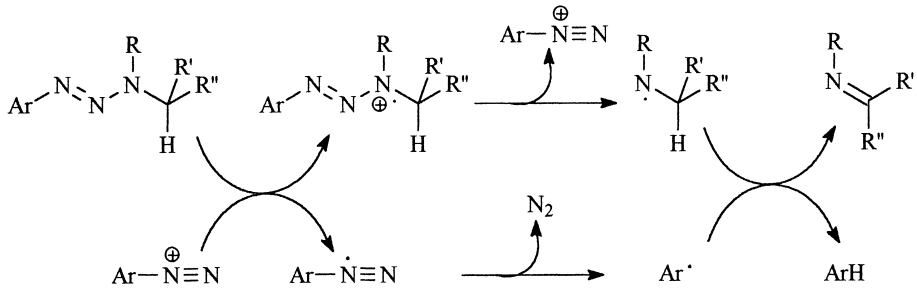
This proposition was corroborated by the influence of the triazene concentration: when the experiment reported in entry 5 (Table 2) was repeated with a higher concentration of triazene (0.43 mol l^{-1} instead of 0.11 mol l^{-1}), the formation of ArF and ArOTf decreased (respective yields: 10 and 8%) whereas ArH was extensively produced (yield = 12%). Such a hypothesis was also consistent with the influence of the introduction mode of the reactants (Table 2, entries 1–3). During procedure B, the triazene was first completely protonated by strong triflic acid; during procedure A, the triazene was probably incompletely protonated by the weaker acid HF/HF_2^-, in procedure C, triflic acid and HF competed for the protonation of the triazene. The same trends were observed in trifluoroethanol (Table 2, entries 4–5) where all reactive species were soluble: radical processes mainly occurred with procedure A. Thus, reduction of the diazonium moiety by the non-protonated triazene can be proposed and rationalised as follows (Scheme 4).

When a deficiency of CsF (0.2 eq) and a slight excess of auxiliary acid (required stoichiometry: 2.0 eq of H^+) was used in CCl_4, procedure A delivered again the best yield of ArF. However, only traces of ArH were detected whatever the procedure (Table 3). This is probably due to a greater acidity of the medium, which was buffered by a smaller amount of fluoride anions (HF only is formed, instead of $HF + HF_2^-$), and, consequently, there is a better protonation of the triazene.

It must be also noticed, from Table 3, that oleum was the best auxiliary acid. As 1.5 equivalent of sulfuric acid was sufficient, it acted as a diacid. Larger amounts decreased the yield of fluoroarene, probably because HF was partly complexed by sulfur trioxide to form fluorosulfonic acid and, consequently, was not available for fluorination. If triflic acid delivered lower yields of ArF than sulfuric acid, it could be due to its higher acidity and its larger ability to protonate HF and form H_2F^+ which is not an efficient fluorinating agent.

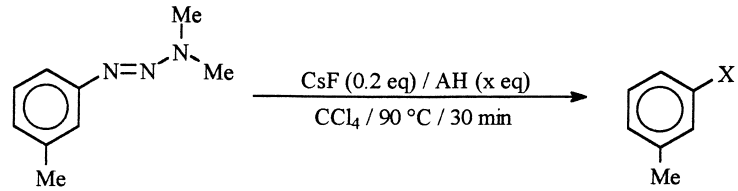
All the above-reported experiments were carried out in carbon tetrachloride or trifluoroethanol. Other solvents were also evaluated but none of them gave satisfactory results:

- ArH was the major product in THF (through a radical chain process) [25] but also in diglyme or ethyl acetate,



Scheme 4. Reduction of a diazonium group by a triazene.

Table 3
Influence of the introduction of the reaction components (CsF in deficiency)



4 C = 0.11 Mol.L^{-1} X = F, OTf, H, Cl

Acid (*x* eq)	Procedure	ArF (%)	ArH (%)	ArF/ArCl
CF_3SO_3H (2.1 eq)	A	26	Trace	1.3
	C	24	Trace	1.4
Oleum (6 wt.% SO_3) (2.1 eq) (mol/mol)	A	36	Trace	5.9
	C	25	Trace	N.D.[a]
Oleum (6 wt.% SO_3) (1.5 eq) (mol/mol)	A	39	Trace	4.0
	C	33	Trace	2.7

[a] N.D.: not determined.

which are good hydrogen atom donors, as well as in formic acid, known for its reducing properties. Hydrogen abstraction was less pronounced in cyclohexane but, nevertheless, also extensive compared to fluoride incorporation.

- Nucleophilic solvents such as methanol, ethanol (even trichloroethanol), formamide, acetonitrile, nitromethane and DMSO [18] competed too strongly with fluoride to be suitable for fluorodetriazenation.

At the first glance, trifluoroethanol seemed more suitable than carbon tetrachloride because it dissolved all the reactants, often provided better yields of fluoroaromatics and could avoid radical by-products. However, too good yields (>100%) were sometimes obtained in it (Table 4, entry 2) and, finally, we found that this solvent could act as a fluoride source, even in the absence of CsF (Table 4, entry 7). To a lesser extent, ethyl trifluoroacetate (Table 4, entry 4) and trifluoroacetic acid (Table 4, entry 9) behaved in the same way, but triflic acid did not (Table 4, entry 10).

Thus, trifluoroethanol, ethyl trifluoroacetate and trifluoroacetic acid cannot be used as solvents for radiofluorination with ^{18}F. Indeed, when the experiment described in Table 4 (entry 6) was repeated with $Cs^{18}F$ in [^{19}F]trifluoroethanol, no [^{18}F]fluorobenzene but rather [^{19}F]fluorobenzene was formed and the radioactivity was recovered in the solvent front during HPLC. The ability of trifluoroethanol to act as a fluoride donor (Scheme 5) is due to the stabilisation of the resulting carbocation by two other fluorine atoms. The same is true for ethyl trifluoroacetate, though to a lesser extent because of the electron-withdrawing effect of the carboxyl group, but cannot be invoked for triflic acid.

In conclusion, decomposition of 1-aryl-3,3-dialkyltriazenes by strong and non-nucleophilic acids (CF_3SO_3H, H_2SO_4) can be achieved at 90°C in carbon tetrachloride, in the presence of sub-stoichiometric amounts of fluoride anions. Yields of fluoroarenes up to 39% (versus F^-) can be reached under these conditions, within 15–30 min and without contamination of the fluorinated compounds by inseparable by-products. Such conditions and results enable an adaptation to radiofluorination with $^{18}F^-$.

3. Experimental section

Caesium fluoride (from Acros, purity: 99%) was dried at 270°C under atmospheric pressure, cooled under vacuum, weighted in the reaction vessel (made of Teflon PFA®) and stored there at 110°C overnight. Solvents and acids (except sulfuric acid) were freshly distilled and stored over molecular sieves.

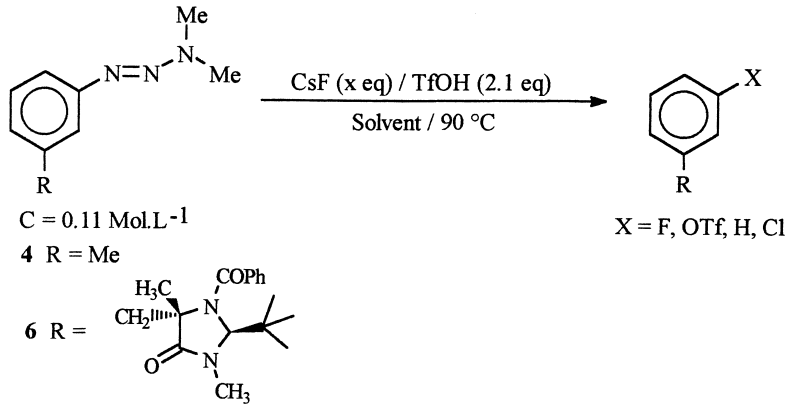
3.1. Procedure A

The solvent CCl_4 (4 ml) was added, through a septum, on CsF (0.18 mmol) conditioned as above and kept under nitrogen. The suspension was cooled at −10°C then triflic acid (1.8 mmol) was added through the septum. The resulting mixture was stirred at −10°C for 5 min then the triazene (0.9 mmol), dissolved in CCl_4 (4 ml), was dropped in. After this final addition, the vessel was tightly closed, kept 5 min more at −10°C then immersed in an oil bath preheated at 90°C. The reaction medium was held at this temperature under magnetic stirring.

3.2. Procedure B

As above, the triazene (0.9 mmol) and CCl_4 (8 ml) were introduced through a septum into the empty vessel kept under nitrogen. After cooling at −10°C, triflic acid

Table 4
Influence of the solvent



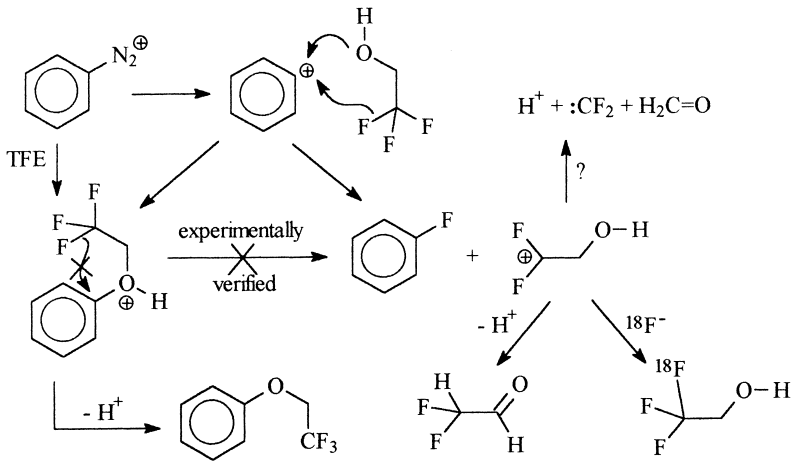
Entry	Substrate	Solvent[a]	Procedure	CsF (eq)	Time (h)	ArF (%)[b]	ArOTf (%)	ArH (%)	Ar–Solvent (%)
1	**4**	CCl_4	C	0.2	0.5	26	74	Trace	–[c]
2	**4**	TFE	C	0.2	0.5	110	N.D.	1	N.D.
3	**4**	ETFA	A	0.2	0.25	7.2	39	Trace	–
4	**4**	ETFA	A	0	0.25	7.1	N.D.	Trace	–
5	**6**	CCl_4	C	0.2	0.5	31	93	0	–[c]
6	**6**	TFE	C	0.2	1	30	11	0	60
7	**6**	TFE	C	0	0.25	30	18	0	56
8	**6**	TFA	A	0.2	0.25	8	N.D.	N.D.	N.D.
9	**6**	TFA	A	0	24	4	N.D.	N.D.	N.D.
10	**6**	TfOH	C	0	0.5	0	25[d]	0	25[d]

[a] TFE: trifluoroethanol; ETFA: ethyl trifluoroacetate; TFA: trifluoroacetic acid.
[b] Versus CsF.
[c] ArCl not determined.
[d] Isolated yield.

(1.8 mmol) was dropped in and the resulting mixture was kept under stirring at this temperature for 5 min. Then the septum was removed as briefly as possible to introduce, under a stream of nitrogen, CsF (0.18 mmol) which was previously conditioned as indicated. After this final addition, the vessel was tightly closed, kept 5 min more at −10°C then immersed for the required time in an oil bath preheated at 90°C.

3.3. Procedure C

The triazene (0.9 mmol), dissolved in CCl_4 (8 ml), was added, through a septum, onto CsF (0.18 mmol) conditioned as above and kept under nitrogen. The suspension was cooled at −10°C then triflic acid (1.8 mmol) was dropped through the septum. The resulting mixture was stirred at −10°C for 5 min then the vessel was tightly closed, kept



Scheme 5. Trifluoroethanol as fluoride source.

5 min more at −10°C and immersed for the required time in an oil bath preheated at 90°C.

3.4. Common work up

After cooling, 0.3 M aqueous KOH (5 ml) was added and the two phases were separated. The aqueous phase was extracted with ethyl ether (3 × 5 ml) and the collected organic phases were washed with water (3 × 5 ml), dried over Na_2SO_4 and filtered.

3.5. Analyses

Most of reaction media were analysed by GC with an internal standard (4-chlorofluorobenzene) against which most of the simplest products have been calibrated. These products were either commercially available or prepared according to the literature (4-methyltriflate, 4-(trifluoroethoxy)acetophenone). Some reaction media were also analysed by ^{19}F NMR with an internal standard ($PhOCF_3$).

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