Trifluoromethanesulfonic acid: a novel solvent for the electrophilic fluorination of fluoroaromatics

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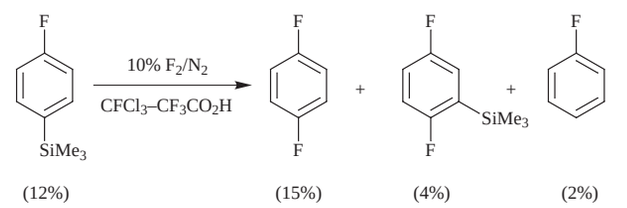
Trifluoromethanesulfonic acid has been discovered to be an excellent new solvent for promoting the direct elemental fluorination of aromatics. Fluorobenzene has been successfully fluorinated to a mixture of 1,4-difluorobenzene (31%) and 1,2-difluorobenzene (7%) in $CFCl_3$–CF_3SO_3H (5%), but no further improvement is observed by the addition of boron trifluoride. When the reaction is carried out in only $CFCl_3$, the main reaction pathway is the 1,2- and 1,4-addition of fluorine to fluorobenzene forming cyclohexenes of molecular formula $C_6H_5F_5$, and only a small amount of 1,4-difluorobenzene is produced. Although both 1,2- and 1,3-difluorobenzene are fluorinated to 1,2,4-trifluorobenzene in $CFCl_3$–CF_3SO_3H (10%), 1,4-difluorobenzene does not undergo the same electrophilic substitution reaction.

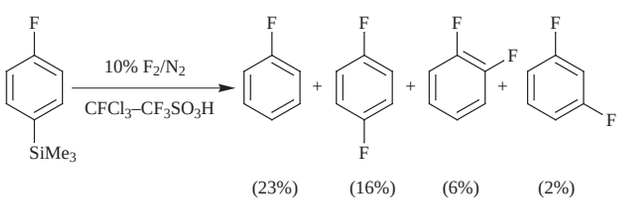
Introduction

The constantly expanding number of pharmaceuticals and agrochemicals which contain fluoroaromatics, both available and currently in research, reflects the increasingly important role of fluorine substitution in aromatics.[1–4] Most of the benefits associated with fluorine are because of its small size coupled with its high electronegativity. Based on van der Waals radii (H 1.20 Å, F 1.47 Å, O 1.52 Å),[5] it can be concluded that fluorine and oxygen are nearly isosteric. Consequently, the replacement of a hydroxy group by fluorine or an ether linkage by CF_2 is often utilised in drugs and agrochemicals. Similarly, substitution of fluorine for hydrogen will not dramatically alter the steric bulk of the molecule. However, it is the electronic effects associated with fluorine which frequently alter the chemical reactivity of organic compounds substituted with it and the advantage of fluorine's strong electron-withdrawing effect is utilised in drug design to block oxidative metabolism. This leads to better and longer activity of drugs *in vivo*, as well as avoiding the problem that many products of oxidative metabolism are toxic. The oxidative metabolism of phenyl rings is such a common problem that fluorine substitution in the 4-position is now common practice in most drug classes where this can be applied.[6] Another consideration in drug design is the rate of absorption and transport of drugs *in vivo* and both aromatic fluorination and fluorination adjacent to most atoms or groups with π electrons is found to increase their lipid solubilities.

We, amongst others,[7,8] are particularly interested in developing the use of elemental fluorine as a selective fluorinating reagent for the direct synthesis of fluoroaromatics. Recently, we reported the *ipso* electrophilic substitution of the trimethylsilyl group in fluoro- and difluoro-phenyltrimethylsilanes with elemental fluorine[9] and as well as catalysing the reaction with boron trifluoride (BF_3·$2CH_3CO_2H$ or BF_3·MeOH) in $CFCl_3$–MeOH (10%), the mixed solvent system $CFCl_3$–CF_3CO_2H (10%) was also discovered to be quite good at promoting this reaction (Scheme 1). However, when the trifluoroacetic acid was replaced with trifluoromethanesulfonic (triflic) acid, and 4-fluorophenyltrimethylsilane was then reacted with 10% fluorine in nitrogen, all of the products were fluorobenzenes with no fluorophenyltrimethylsilanes present (Scheme 2). We believed that protodesilylation had occurred in this stronger acid giving fluorobenzene (23%), which was subsequently fluorinated to 1,4-difluorobenzene (16%), 1,2-difluorobenzene (6%) and 1,3-difluorobenzene (2%). Here, we confirm this proposal by reporting a novel mixed solvent system, which requires only 5–10% of triflic acid present in $CFCl_3$, for promoting the electrophilic fluorination of fluorobenzene, 1,2-difluorobenzene and 1,3-difluorobenzene.



Scheme 1 Fluorination of 4-fluorophenyltrimethylsilane in $CFCl_3$–CF_3CO_2H (10%)

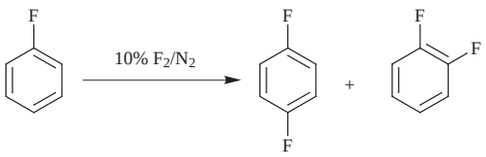


Scheme 2 Fluorination of 4-fluorophenyltrimethylsilane in $CFCl_3$–CF_3SO_3H (10%)

Results and discussion

When fluorine, diluted with nitrogen, was bubbled through fluorobenzene instead of 4-fluorophenyltrimethylsilane in the mixed solvent system $CFCl_3$–CF_3SO_3H (5%) the yield of 1,4-difluorobenzene doubled to 31% and 1,2-difluorobenzene was produced in only 7% yield (Table 1). The same reaction proceeded slower with less conversion of fluorobenzene (22% remaining) when it was catalysed with boron trifluoride (BF_3·$2CH_3CO_2H$, 1.2 equiv.). Only a 20% yield of 1,4-difluorobenzene was obtained giving a similar result to the fluorination of 4-fluorophenyltrimethylsilane. A control reaction was also carried out with boron trifluoride (BF_3·$2CH_3CO_2H$, 1.2 equiv.) present but in the absence of triflic acid. Although small amounts of fluorobenzene (10 area%), 1,4-difluorobenzene (3 area%) and 1,2-difluorobenzene (1 area%) were observed,

Table 1 Elemental fluorinations of fluorobenzene

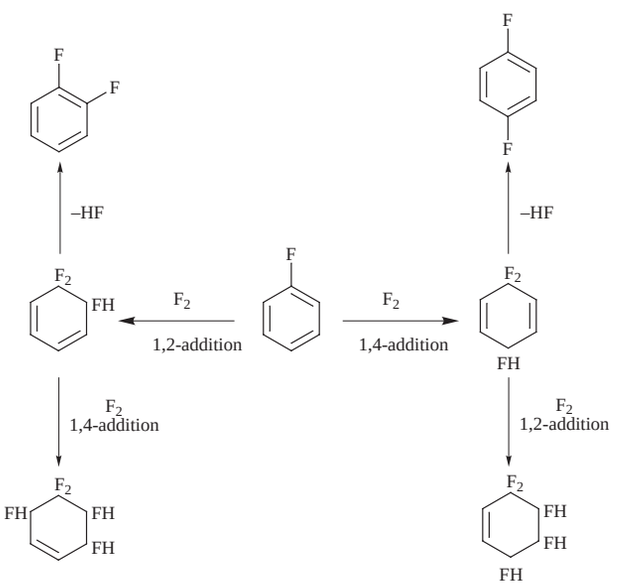


III **I** **II**

Solvent system	F_2 (Equiv.)	*T*/°C	Yield (%)[a] I	II	III
$CFCl_3$–CF_3SO_3H (5%)	1.1	−30	31 (2.1)	7 (0.5)	7 (1.0)
$CFCl_3$–CF_3SO_3H (5%) BF_3 (1.2 equiv.)	1.1	−25	20 (0.9)	7 (0.3)	22 (1.0)
$CFCl_3$–CF_3CO_2H (10%)	1.5	−5	8 (0.4)	3 (0.2)	16 (1.0)
$CFCl_3$–CF_3CO_2H (50%)	1.1	−20	16 (0.7)	6 (0.3)	24 (1.0)
CH_2Cl_2–CF_3CO_2H (50%)	1.1	−15	2 (0.02)	0 (0)	67 (1.0)
CH_3CN–CF_3SO_3H (10%)	1.1	−30	9 (0.3)	6 (0.2)	29 (1.0)

[a] ^{19}F NMR mole ratios are shown in parentheses.

the reaction was extremely poor with 12 by-products observed in 1–6 area% yield in the GC and *ca*. 18 signals were observed in the aromatic region of the ^{19}F NMR spectrum as well as 9 signals between −180 and −220 ppm, which are characteristic of fluoroalkanes. Some of our earlier work had already shown that the main reaction pathway in the uncatalysed elemental fluorination of fluorobenzene in $CFCl_3$ was the 1,2- and 1,4-addition of fluorine to fluorobenzene resulting in the formation of two cyclohexenes of molecular formula $C_6H_5F_5$ (Scheme 3)



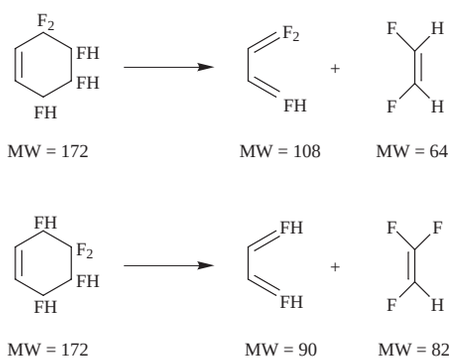
Scheme 3 1,2- and 1,4-addition of fluorine to fluorobenzene

and only a small amount of 1,4-difluorobenzene was produced (Table 2). The cyclohexenes were identified by their fragmentation pattern in the GC-MS, where they formed butadienes by a reverse Diels–Alder reaction (Scheme 4). The cyclohexene, $C_6H_4F_6$, was also produced by the same 1,2- and 1,4-addition of fluorine to 1,4-difluorobenzene. It can therefore be concluded that the triflic acid plays a vital role in the monofluorination of fluorobenzene.

At this stage it is unknown whether the triflic acid is catalysing the electrophilic fluorination by strongly polarising the F–F bond or whether the triflic acid is fluorinated to form the hypofluorite (CF_3SO_3F) *in situ*, which in turn fluorinates the fluorobenzene. However, from the distribution of isomers formed in the elemental fluorinations of fluorobenzene in $CFCl_3$–CF_3SO_3H, it seems most probable that these reactions

Table 2 Elemental fluorination of fluorobenzene in $CFCl_3$

Product	Yield (area%)
C_6H_5F	86.2
1,4-$C_6H_4F_2$	3.0
$C_6H_4F_6$ + $C_6H_5F_5$	2.0
$C_6H_5F_5$	3.6
$C_6H_5F_5$	5.3

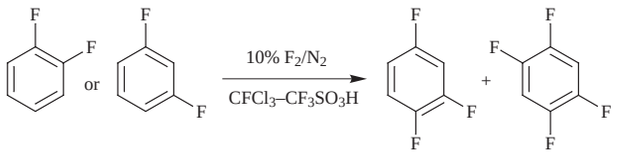


Scheme 4 Reverse Diels–Alder reaction of cyclohexenes

are proceeding by an electrophilic substitution mechanism. It is well recognised that although fluorobenzene undergoes both *ortho* and *para* electrophilic substitution, it is *para* substitution which dominates and this can be explained by considering the electronic effects of fluorine. Not only does it have a pronounced sigma electron withdrawing effect, $-I_\sigma$, but when attached to a π system it can also back donate electrons in an I_π repulsive interaction. Consequently in both the nitration (4-fluoronitrobenzene : 2-fluoronitrobenzene = 1 : 0.14)[10] and Friedel–Crafts benzylation (4-product : 2-product = 1 : 0.18) of fluorobenzene the 4-isomer dominates[11] and the elemental fluorination of fluorobenzene in $CFCl_3$–CF_3SO_3H (5%) gives a similar ratio (1 : 0.22) of 1,4-difluorobenzene : 1,2-difluorobenzene. The relative amount of 1,2-difluorobenzene produced was slightly more when the reaction was catalysed with boron trifluoride (1 : 0.35).

In the light of the effective fluorodesilylations in $CFCl_3$–CF_3CO_2H (10%) we reported earlier,[9] trifluoroacetic acid was also investigated as a potential acid for the direct elemental fluorination of fluorobenzene (Table 1). Although the reaction was slower in $CFCl_3$–CF_3CO_2H (10%) than in $CFCl_3$–CF_3SO_3H (5%), the 1,4-difluorobenzene : 1,2-difluorobenzene ratio was 1 : 0.44, which was similar to the fluorinations in triflic acid suggesting that a similar mechanism was occurring. However,

Table 3 Elemental fluorinations of 1,2-difluorobenzene and 1,3-difluorobenzene (FB = Fluorobenzene)

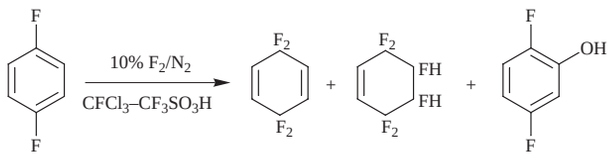


VI IV V

Substrate	F_2 (equiv.)	*T*/°C	CF_3SO_3H (%)	Volume/ cm^3	Conversion (%) IV	V	VI
1,2-Di-FB	1.1	−20	5	200	13	2	10
1,2-Di-FB	1.1	−25	10	100	13	2	6
1,3-DiFB	1.1	−15	10	100	18	2	6

there was a much lower accountability of main products because more by-products were formed and it was not such a selective reaction. By increasing the amount of trifluoroacetic acid present to 50% the reaction rate was increased despite lowering both the reaction temperature and the amount of fluorine passed through the reaction mixture. There was still less conversion to 1,4-difluorobenzene than in the corresponding fluorination in $CFCl_3$–CF_3SO_3H (5%), but most surprisingly, when the same reaction was carried out in CH_2Cl_2–CF_3CO_2H (50%) there was hardly any conversion to 1,4-difluorobenzene. Coenen and Moerlein[12] reported reduced fluorodestannylation yields with both elemental fluorine and acetyl hypofluorite when the solvent was changed from $CFCl_3$ or CCl_4 to hydrogen-containing CH_2Cl_2, but when the solvent contained methyl group(s) *e.g.* acetonitrile, dimethyl sulfoxide, they discovered that the fluorination was completely inhibited. In contrast to this, although dichloromethane inhibited the fluorination of fluorobenzene, it was possible to obtain fluorination with reduced yields when $CFCl_3$ was substituted for dry acetonitrile (Table 1). These results are more in agreement with Rozen's work,[13] when he tried to find alternative solvents to $CFCl_3$ for the synthesis and reactions of acetyl hypofluorite. Although he found that acetonitrile can replace $CFCl_3$ satisfactorily, only a low concentration of acetyl hypofluorite (<5 mM) was obtained in $CHCl_3$–CH_3CO_2H (10 : 1). We also tried one experiment using 10% concentrated sulfuric acid in $CFCl_3$ at 2 °C. The reaction completely over-fluorinated with no fluorobenzene left and although both 1,4- and 1,2-difluorobenzene were present, many other compounds were observed in both the GC and ^{19}F NMR spectrum. Due to the number of products in this reaction the use of concentrated sulfuric acid was not investigated further. In hindsight, this was not a surprising result because Chambers[7] has reported that a high degree of fluorination can be obtained on reacting fluorine with deactivated aromatics in concentrated sulfuric acid and the above reaction involves using a more activated aromatic system. Subsequently, we have shown that the fluoroarenes slowly react with concentrated sulfuric acid under our reaction conditions making its use as a solvent for fluorination impossible.

The main product in the direct elemental fluorination of 1,2-difluorobenzene in $CFCl_3$–CF_3SO_3H (5 or 10%) was 1,2,4-trifluorobenzene (13%) and its subsequent fluorination produced 1,2,4,5-tetrafluorobenzene in 2% yield (Table 3). Unfortunately less fluorination occurred and there was a much lower accountability of fluoroaromatics than in the fluorination of fluorobenzene because the reaction displayed lower selectivity with more by-products produced. A similar result was also obtained in the direct elemental fluorination of 1,3-difluorobenzene (Table 3) in $CFCl_3$–CF_3SO_3H (10%). Because of the directing effects of the fluorine substituents reinforcing each other to the same position on the ring a slightly higher conversion to 1,2,4-trifluorobenzene (18%) was achieved and a small amount of 1,2,4,5-tetrafluorobenzene (2%) was also observed. The fluorination of 1,4-difluorobenzene in $CFCl_3$–CF_3SO_3H (10%) was not as successful as the fluorination of 1,2- or 1,3-difluorobenzene (Scheme 5). With the strong *para*-



VII 2 x VIII IX

Scheme 5 Fluorination of 1,4-difluorobenzene in $CFCl_3$–CF_3SO_3H (10%)

directing effect of the fluorine substituent and the *para* position being blocked by another fluorine substituent in 1,4-difluorobenzene, the main reaction pathway was the 1,4-addition of fluorine to produce cyclohexadiene **VII**, $C_6H_4F_4$. This was followed by the 1,2-addition of fluorine to form the main products, which were two cyclohexenes of molecular formula, $C_6H_4F_6$. Only a very small amount of 1,2,4-trifluorobenzene and a trace of 1,2,4,5-tetrafluorobenzene were observed in the ^{19}F NMR spectrum as well as some of the starting material. A difluorophenol was also produced in the reaction and this implied that water must have either reacted directly with the carbocation formed or reacted with fluorine to form hypofluorous acid, HOF, which is a powerful hydroxylating agent.[14]

A major problem we found in all of this work was the clean separation of the aromatic material from solvent. We found, somewhat to our surprise, that most fluoroarenes form azeotropes with CCl_3F, and this coupled with their very high vapour pressure at room temperature led in many cases to a low recovery of the fluoroarenes when we attempted to isolate the products. This led us to develop a GC and an NMR method to determine the weight percentages of our products in the mixtures and the product ratios respectively (see Experimental section for details).

In conclusion, our work compares favourably with the work on liquid phase fluorinations of aromatics reported by both Napoli[8] and Chambers.[7] Napoli agreed with Rozen's original work and reported that the more polar solvents encouraged the monofluorination of aromatics.[8] He deduced the following decreasing order of solvents derived from the elemental fluorinations of benzene, toluene, phenol and benzoic acid $CF_3CO_2H > CF_3CH_2OH > CH_3OH > CHCl_3 > CFCl_3$. Although Napoli's best results were obtained in trifluoroacetic acid, he observed that it was essential to keep the conversion of the starting material below 50% as above this the yields of monofluorinated products dropped considerably. More recently Chambers *et al.*[7] discovered that formic acid is an excellent medium for the room temperature elemental fluorination of *para*-substituted deactivated aromatics whose substituent directional effects reinforce each other. For example, 3,4-difluorobenzoic acid was obtained in 66% yield from a 79% conversion of 4-fluorobenzoic acid. Remarkably, concentrated sulfuric acid was found to further increase the reactivity of fluorine and a much higher degree of fluorination could be achieved in it. For example, pentafluorobenzoic acid could be produced by the reaction of fluorine with 2,4-difluorobenzoic acid in concentrated sulfuric acid at room temperature. We have also independently discovered that an acid, trifluoromethanesulfonic acid, plays a vital role in promoting the electrophilic fluorination of the more activated aromatic, fluorobenzene, and it is much superior to trifluoroacetic acid in this role. The advantage of this system over previous work is that only 5–10% of triflic acid is required in $CFCl_3$ to promote the reaction. However, all three groups have shown that acids will probably become the best solvents for the direct elemental

fluorination of aromatics in the future and it seems certain that some acids will be discovered to be excellent at promoting the fluorination of deactivated aromatics whilst others will be better at promoting the monofluorination of activated aromatics.

Experimental

The ^1H and ^{13}C NMR spectra were recorded on a Bruker AC300 NMR spectrometer in $CDCl_3$. Chemical shifts are reported in parts per million (δ in ppm) downfield from internal tetramethylsilane. ^{19}F NMR spectra were recorded on a JEOL FX90Q spectrometer using $CDCl_3$ as the solvent with chemical shifts (δ in ppm) downfield from internal $CFCl_3$. Gas chromatographic analysis were performed on a Pye Unicam series 304 chromatograph fitted with a WCOT fused silica coating CP-Sil 19CB column (50 m × 0.32 mm i.d.). The GC-MS were recorded on a Kratos Profile mass spectrometer in the electron impact mode.

Methanol was dried using dry magnesium turnings and dichloromethane was distilled over calcium hydride before being stored over 4 Å molecular sieves. Trichlorofluoromethane was also stored over 4 Å molecular sieves in the refrigerator. Ether refers to diethyl ether and was dried over sodium wire. All other chemicals were used as received from suppliers. In the elemental fluorinations 10% fluorine in nitrogen, premixed and provided by Air Products, was used. The fluorine line was set up so that the 10% F_2/N_2 passed through a column of potassium fluoride, to remove any hydrogen fluoride present, before being regulated by a glass flow meter. The elemental fluorinations were conducted in a glass cylindrical reactor which had a side arm to allow the 10% F_2/N_2 to be bubbled through a sintered disc directly into the bottom of the reaction mixture. This left room in the middle of the flask for a Teflon paddle which was connected by a steel shaft to a vibro-stirrer motor and was used for efficient mixing. The reactor was also equipped with a thermocouple pocket and an exit port.

Yields of products, expressed as weight percentages and shown in parentheses in the experiments, were calculated on the basis of using toluene as an internal standard. In the method used the weight percentage of the compound in the unknown sample was calculated using GC response factors calculated in the presence of the internal standard. This method allows the weight percentage of a compound in a mixture, in the presence of a known weight of the internal standard, to be calculated from the relative size of the compound's peak area with respect to the area of that of the internal standard. By using a known weight of hexafluorobenzene as internal standard it was also possible to calculate the product ratio from the ^{19}F NMR spectra of the mixed fluorobenzenes. These two methods were shown to give a reasonably good correlation. The products isolated were mixtures of known fluorobenzenes and they were identified in the mixtures by comparison with known spectral characteristics. To ensure accuracy we in fact isolated samples of the fluorobenzenes produced in the first experiment described below by preparative GC.

Fluorination of fluorobenzene in $CFCl_3$–CF_3SO_3H (5%)
Using the above experimental procedure 10% F_2/N_2 was bubbled at 1 l h^{-1} for 3 h (13 mmol F_2) through fluorobenzene (1.15 g, 12 mmol) in $CFCl_3$ (190 cm^3) and CF_3SO_3H (10 cm^3) at −30 °C. Working the reaction mixture up afforded an oil (1.71 g) from which samples of the fluoroaromatics were isolated by preparative GC and were identified as fluorobenzene, 1,2-difluorobenzene and 1,4-difluorobenzene respectively. The fluoroaromatic mixture was also analysed by ^{19}F NMR, after addition of hexafluorobenzene as an internal standard, which showed that the mixture consisted of fluorobenzene (7%), 1,4-difluorobenzene (31%) and 1,2-difluorobenzene (7%).

Fluorination of fluorobenzene in $CFCl_3$–CF_3SO_3H (5%) and $BF_3{\cdot}2CH_3CO_2H$
Using the same experimental procedure 10% F_2/N_2 was bubbled at 1 l h^{-1} for 3 h (13 mmol F_2) through fluorobenzene (1.15 g, 12 mmol) in $CFCl_3$ (188 cm^3), CF_3SO_3H (10 cm^3) and $BF_3{\cdot}2CH_3CO_2H$ (2.7 g, 14 mmol) at −25 °C. The resulting oil (3.18 g) was analysed by GC, with toluene added as an internal standard, and ^{19}F NMR, with hexafluorobenzene added as an internal standard. The oil was found to consist of fluorobenzene (22%), 1,4-difluorobenzene (20%) and 1,2-difluorobenzene (7%).

Fluorination of fluorobenzene in $CFCl_3$ and $BF_3{\cdot}2CH_3CO_2H$
Using the same experimental procedure 10% F_2/N_2 was bubbled at 1 l h^{-1} for 3 h (13 mmol F_2) through fluorobenzene (1.15 g, 12 mmol) in $CFCl_3$ (198 cm^3) and $BF_3{\cdot}2CH_3CO_2H$ (2 cm^3, 2.7 g, 14 mmol) at −78 °C. Although the oil (0.63 g) was found to contain small amounts of fluorobenzene (10 area %), 1,4-difluorobenzene (3 area %) and 1,2-difluorobenzene (1 area %), the GC also had 12 other peaks in 1–6 area %. Similarly the ^{19}F NMR spectrum had *ca*. 18 signals in the aromatic region (−100 to −140 ppm) as well as 9 signals between −180 and −220 ppm, which are characteristic of fluoroalkanes.

Fluorination of fluorobenzene in $CFCl_3$
Using the same experimental procedure 10% F_2/N_2 was bubbled at *ca*. 0.5 l h^{-1} for 4 h through fluorobenzene (2.0 g, 21 mmol) in $CFCl_3$ (50 cm^3) at −78 °C. The resulting oil (1.2 g) was analysed by GC-MS and as this reaction was the result of some preliminary work, the yields quoted are from the area percent on the GC-MS assuming that all response factors were equal to one. The oil was found to contain fluorobenzene (86 area %); 1,4-difluorobenzene (3 area %); $C_6H_4F_6$: *m*/*z* (EI) 171 $(M - F)^+$, 151 $(M - HF_2)^+$, 126 $(M - C_2H_2F_2 = C_4H_2F_4)^+$, 108 $(M - C_2HF_3 = C_4H_3F_3)^+$; and $C_6H_5F_5$ (2 area %): *m*/*z* (EI) 172 (M^+), 108 $(M - C_2H_2F_2 = C_4H_3F_3)^+$, 90 $(M - C_2HF_3 = C_4H_4F_2)^+$; $C_6H_5F_5$ (4 area %): *m*/*z* (EI) 172 (M^+), 133 $(M - HF_2)^+$, 108 $(M - C_2H_2F_2 = C_4H_3F_3)^+$; and $C_6H_5F_5$ (5 area %): *m*/*z* (EI) 172 (M^+), 153 $(M - F)^+$, 139 $(M - HF_2)^+$, 133 $(M - HF_2)^+$, 108 $(M - C_2H_2F_2 = C_4H_3F_3)^+$, 90 $(M - C_2HF_3 = C_4H_4F_2)^+$.

Fluorination of fluorobenzene in $CFCl_3$–CF_3CO_2H (10%)
Using the same experimental procedure 10% F_2/N_2 was bubbled at 1 l h^{-1} for 3 h (13 mmol F_2) through fluorobenzene (1.15 g, 12 mmol) in $CFCl_3$ (180 cm^3) and CF_3CO_2H (20 cm^3) at −5 °C. The resulting oil (2.41 g) was analysed by GC, with toluene added as an internal standard, and ^{19}F NMR, with hexafluorobenzene added as an internal standard. The oil was found to consist of fluorobenzene (16%), 1,4-difluorobenzene (8%) and 1,2-difluorobenzene (3%).

Fluorination of fluorobenzene in $CFCl_3$–CF_3CO_2H (50%)
Using the same experimental procedure 10% F_2/N_2 was bubbled at 1 l h^{-1} for 3 h (13 mmol F_2) through fluorobenzene (1.15 g, 12 mmol) in $CFCl_3$ (100 cm^3) and CF_3CO_2H (100 cm^3) at −20 °C. The resulting oil (2.1 g) was analysed by GC and ^{19}F NMR and consisted of fluorobenzene (28 area %), 1,4-difluorobenzene (18 area %) and 1,2-difluorobenzene (7 area %).

Fluorination of fluorobenzene in CH_2Cl_2–CF_3CO_2H (50%)
Using the same experimental procedure 10% F_2/N_2 was bubbled at 1 l h^{-1} for 3 h (13 mmol F_2) through fluorobenzene (1.15 g, 12 mmol) in CH_2Cl_2 (100 cm^3) and CF_3CO_2H (100 cm^3) at −15 °C. The resulting oil (3.0 g) was analysed by GC and ^{19}F NMR and consisted of fluorobenzene (63 area %) and 1,4-difluorobenzene (3 area %).

Fluorination of fluorobenzene in CH_3CN–CF_3SO_3H (10%)
Using the same experimental procedure 10% F_2/N_2 was bubbled at 1 l h^{-1} for 3 h (13 mmol F_2) through fluorobenzene (1.15 g, 12

mmol) in CH_3CN (180 cm^3) and CF_3SO_3H (20 cm^3) at −30 °C. The reaction mixture was worked up by pouring into water (400 cm^3), neutralising with $NaHCO_3$ and then extracting with ether (4 × 75 cm^3). The ethereal extracts were then combined and washed with water (4 × 200 cm^3), dried over $MgSO_4$ and finally the ether was distilled off. The products were then analysed by GC, after addition of toluene as an internal standard, and ^{19}F NMR, after addition of hexafluorobenzene as an internal standard. The oil (9.03 g) consisted of acetonitrile, fluorobenzene (29%), 1,4-difluorobenzene (9%) and 1,2-difluorobenzene (6%).

Fluorination of fluorobenzene in $CFCl_3$–H_2SO_4 (10%)
Using the same experimental procedure 10% F_2/N_2 was bubbled at 1 l h^{-1} for 4 h (18 mmol F_2) through fluorobenzene (1.15 g, 12 mmol) in $CFCl_3$ (180 cm^3) and H_2SO_4 (20 cm^3) at 2 °C. The GC of the resulting oil (1.38 g) consisted of 8 peaks in 8–13 area % and a further 11 peaks in 1–5 area %. Both 1,4- and 1,2-difluorobenzene were present in 12 and 9 area % respectively. The signals for 1,4- and 1,2-difluorobenzene were also observed in the ^{19}F NMR spectrum but many other unidentified products were also present.

Fluorination of 1,2-difluorobenzene in $CFCl_3$–CF_3SO_3H (5%)
Using the same experimental procedure 10% F_2/N_2 was bubbled at 1 l h^{-1} for 3 h (13 mmol F_2) through 1,2-difluorobenzene (1.39 g, 12 mmol) in $CFCl_3$ (190 cm^3) and CF_3SO_3H (10 cm^3) at −20 °C. The reaction mixture was worked up and the resulting oil was analysed by GC, after addition of toluene as an internal standard, and ^{19}F NMR, after addition of hexafluorobenzene as an internal standard. The oil was found to consist of 1,2-difluorobenzene (10%); 1,2,4-trifluorobenzene (13%): [δ_F − 116.1 (1F, m, 4-F), −133.8 (1F, m, 2-F), −143.8 (1F, m, 1-F); *m/z* (EI) 132 (M^+), 101 ($M - F)^+$, 88 ($M - C_2HF)^+$, 81 ($M - CHF_2)^+$, 63 ($M - CF_3)^+$]; and 1,2,4,5-tetrafluorobenzene (2%): [δ_F − 139.7 (4F, virtual triplet, $^3J_{FH} \approx {}^4J_{FH}$ 8.5); *m/z* (EI) 150 (M^+), 130 ($M - HF)^+$, 119 ($M - CF)^+$, 99 ($M - CHF_2)^+$, 81 ($M - CF_3)^+$].

Fluorination of 1,2-difluorobenzene in $CFCl_3$–CF_3SO_3H (10%)
Using the same experimental procedure 10% F_2/N_2 was bubbled at 1 l h^{-1} for 3 h (13 mmol F_2) through 1,2-difluorobenzene (1.39 g, 12 mmol) in $CFCl_3$ (90 cm^3) and CF_3SO_3H (10 cm^3) at −25 °C. The reaction mixture was worked up and the resulting oil was analysed by GC, after addition of toluene as an internal standard, and ^{19}F NMR, after addition of hexafluorobenzene as an internal standard. The oil was found to consist of 1,2-difluorobenzene (6%), 1,2,4-trifluorobenzene (12%) and 1,2,4,5-tetrafluorobenzene (2%).

Fluorination of 1,3-difluorobenzene in $CFCl_3$–CF_3SO_3H (10%)
Using the same experimental procedure 10% F_2/N_2 was bubbled at 1 l h^{-1} for 3 h (13 mmol F_2) through 1,3-difluorobenzene (1.40 g, 12 mmol) in $CFCl_3$ (90 cm^3) and CF_3SO_3H (10 cm^3) at −15 °C. The reaction mixture was worked up and the resulting oil was analysed by GC, after addition of toluene as an internal standard, and ^{19}F NMR, after addition of hexafluorobenzene as an internal standard. The oil was found to consist of 1,3-difluorobenzene (6%), 1,2,4-trifluorobenzene (19%) and 1,2,4,5-tetrafluorobenzene (1%).

Fluorination of 1,4-difluorobenzene in $CFCl_3$–CF_3SO_3H (10%)
Using the same experimental procedure 10% F_2/N_2 was bubbled at 1 l h^{-1} for 3 h (13 mmol F_2) through 1,4-difluorobenzene (1.38 g, 12 mmol) in $CFCl_3$ (190 cm^3) and CF_3SO_3H (10 cm^3) at −25 °C. The reaction mixture was worked up and the resulting oil was analysed by GC-MS. The oil was found to consist of tetrafluorobenzene: *m/z* (EI) 150 (M^+), 130 ($M - HF)^+$, 119 ($M - CHF_2)^+$, 99 ($M - CHF_2)^+$, 81 ($M - CF_3)^+$; $C_6H_4F_4$: *m/z* (EI) 133 ($M - F)^+$, 126 ($M - C_2H_2$), 113 ($M - HF_2)^+$, 108 ($M - C_2HF)^+$, 83 ($M - CF_3)^+$; $C_6H_4F_6$: *m/z* (EI) 171 ($M - F)^+$, 151 ($M - HF_2)^+$, 150 ($M - H_2F_2)^+$, 139 ($M - CHF_2)^+$, 126 ($M - C_2H_2F_2)^+$, 121 ($M - CF_3)^+$, 108 ($M - C_2HF_3)^+$; 1,2,4-trifluorobenzene; $C_6H_4F_6$: *m/z* (EI) 190 (M^+), 171 ($M - F)^+$, 151 ($M - HF_2)^+$, 139 ($M - CHF_2)^+$, 126 ($M - C_2H_2F_2)^+$, 121 ($M - CF_3)^+$, 108 ($M - C_2HF_3)^+$; 1,4-difluorobenzene and $C_6H_3F_2OH$: *m/z* (EI) 130 (M^+), 111 ($M - F)^+$, 104 ($M - C_2H_2)^+$, 102 ($M - CO)^+$, 83 ($M - COF)^+$, 76 ($M - CO - C_2H_2)^+$.

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References

1 R. E. Banks, *Organofluorine Chemicals and their Industrial Applications*, Ellis Horwood, Chichester UK, 1979.
2 R. E. Banks, *Preparation, Properties and Industrial Applications of Organofluorine Compounds*, Ellis Horwood, Chichester UK, 1982.
3 R. E. Banks, B. E. Smart and J. C. Tatlow, *Organofluorine Chemistry: Principles and Commercial Applications*, Plenum Press, New York, 1994.
4 R. Filler and Y. Kobayashi, *Biomedicinal Aspects of Fluorine Chemistry*, Elsevier, Amsterdam, 1982.
5 A. Bondi, *J. Phys. Chem.*, 1964, **68**, 441.
6 A. B. McElroy, *Applications of Fluorine in Medicinal Chemistry*, Proceedings of Fluorine in Medicine in the 21st Century, UMIST, 1994.
7 (*a*) R. D. Chambers, C. J. Skinner, J. Thomson and J. Hutchinson, *J. Chem. Soc.*, *Chem. Commun.*, 1995, 17; (*b*) R. D. Chambers, C. J. Skinner, J. Hutchinson and J. Thomson, *J. Chem. Soc.*, *Perkin Trans. 1*, 1996, 605.
8 L. Conte, G. P. Gambaretto, M. Napoli, C. Fraccaro and E. Legnaro, *J. Fluorine Chem.*, 1995, **70**, 175.
9 A. M. Stuart, P. L. Coe and D. J. Moody, *J. Fluorine Chem.*, 1998, **88**, 179.
10 G. A. Olah, S. J. Kuhn and S. H. Flood, *J. Am. Chem. Soc.*, 1961, **83**, 4581.
11 G. A. Olah, S. J. Kuhn and S. H. Flood, *J. Am. Chem. Soc.*, 1962, **84**, 1695.
12 H. H. Coenen and S. M. Moerlein, *J. Fluorine Chem.*, 1987, **36**, 63.
13 S. Rozen, Y. Bareket and M. Kol, *J. Fluorine Chem.*, 1993, **61**, 141.
14 S. Rozen, M. Brand and M. Kol, *J. Am. Chem. Soc.*, 1989, **111**, 3325.

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