N-Halogeno compounds. Part 18. 1-Alkyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane salts: user-friendly site-selective electrophilic fluorinating agents of the *N*-fluoroammonium class[1]

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Methods of synthesis are described for a range of 1-alkyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane salts $[R\text{-}N^{+}(CH_2CH_2)_3N^{+}\text{-}F\ (X^{-})_2$, where R = CH_3, CH_2Cl, C_2H_5, CF_3CH_2, C_8H_{17} and $(X^{-})_2$ = $(TfO^{-})_2$, $(BF_4^{-})_2$, $(PF_6^{-})_2$, (TfO^{-}, BF_4^{-}), (TfO^{-}, PF_6^{-}), (TfO^{-}, FSO_3^{-})] by direct fluorination (with neat F_2 at $\leqslant 20$ mmHg or F_2–N_2 blends at 1 atm pressure) of monoquaternary salts of 1,4-diazabicyclo[2.2.2]octane $[R\text{-}^{+}N(CH_2CH_2)_3N\ X^{-}]$ or their 1:1 adducts with boron trifluoride, phosphorus pentafluoride, or sulfur trioxide in acetonitrile at *ca* −35 °C. The results of site-selective electrophilic fluorination of diethyl sodio(phenyl)malonate [⟶ $PhCF(CO_2Et)_2$], 1-morpholinocyclohexene (⟶ 2-fluorocyclohexanone), phenol (⟶ 2- and 4-FC_6H_4OH), 1- and 2-hydroxynaphthalene (⟶ 2- and 4-$FC_{10}H_6OH$, and 1-$FC_{10}H_6OH$ and 1,1-difluoro-2-oxo-1,2-dihydronaphthalene, respectively), acetanilide (⟶ 2- and 4-$FC_6H_4NHCOCH_3$), anisole (⟶ 2- and 4-$FC_6H_4OCH_3$) and sodium benzenesulfinate (⟶ $PhSO_2F$) with these *N*-fluoroammonium salts are presented.

Although a sizeable arsenal of fluorinating agents is available to organic chemists nowadays,[2] practitioners of C–F bond synthesis are often frustrated by the shortcomings of reagents belonging to both the F^{-} and the F^{+} delivery classes,† particularly when site-selective fluorination (including ^{18}F placement[4]) of biologically active molecules is being pursued.[5] In the case of electrophilic fluorination,[2a,c] the search for more generally acceptable (less aggressive, nonexplosive, less toxic, relatively inexpensive) reagents than perchloryl fluoride, O–F compounds like trifluoromethyl hypofluorite or caesium fluoroxysulfate, xenon difluoride or fluorine itself[6] has centred for some time now on compounds of the N–F class, the potential of which was first signalled more than thirty years ago through work on perfluoro-*N*-fluoropiperidine **1** by Banks and Williamson.[7] Triggered by reports in 1983–1984 on the synthesis and electrophilic fluorination capabilities of *N*-fluoropyridin-2(1*H*)-one **2** (Purrington's reagent)[8] and *N*-fluoro-*N*-alkylsulfonamides **3** (Barnette reagents),[9] a renaissance of research activity in the area soon led to almost simultaneous reports on the more reactive[10] reagents *N*-fluoropyridinium salts (*e.g.* **4**; Umemoto reagents)[11] and *N*-fluoroquinuclidinium fluoride **5a**,[12] and to the introduction of the yet more powerful[10] 'F^{+}' transfer agent *N*-fluorobis(trifluoromethylsulfonyl)imide **6** (DesMarteau's reagent).[13] Continuing activity in the area[2a,c] has resulted in a healthy list of N–F reagents, several of which [notably **3** (R = Me or Pr), **4** (and analogues), **5b**, **7**, **8** and **10**] are now available commercially.[14]

The object of the present paper is to provide a full account[1] of the conception, laboratory synthesis and original site-selective 'F^{+}' transfer fluorinations associated with the development of easily-handled crystalline 1-alkyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane salts **9a–k** and **10**,[15] the last of which is produced nowdays on a multi-tonne scale for use primarily in the pharmaceutical industry.[16a] Interestingly, the manufacture of **10**, widely known as Selectfluor™ Reagent F–TEDA–BF_4 (TEDA = triethylenediamine), provides only the second example of the use of difluorine at plant level to effect the site-selective monofluorination of a 'complex' organic substrate, the other being the production of the famous anticancer agent 5-fluorouracil.[2a]

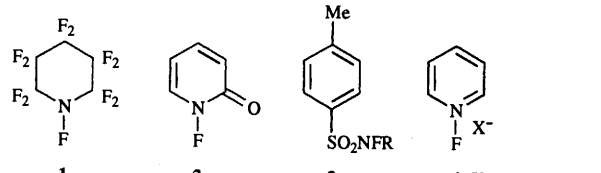
† This applies even to actual (as distinct from incipient) F^{-} sources (*e.g.* see ref. 3).

Background to the development of F–TEDA reagents[17]

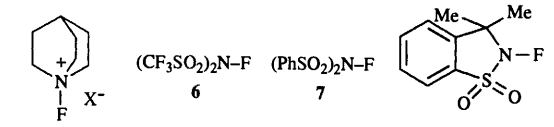
The serendipitous discovery of *N*-fluoroquinuclidinium fluoride NFQnF **5a** by Du Boisson and Morton and its subsequent development as a user-friendly 'F^{+}'-transfer agent,[12,18] including improved synthesis methodology and the introduction of virtually non-hygroscopic variants (**5b–d**),[19] inspired our work on the direct fluorination of the much more readily available and cheaper bridgehead amine 1,4-diazabicyclo-[2.2.2]octane, known in the polyurethane foam industry as TEDA (triethylenediamine). Not only, it was argued, ought a 'bis-analogue' **11** of an NFQnX reagent **5** be more cost-effective (greater mass% of available 'F^{+}'), but also it would provide a more powerful means of site-selective fluorination through the electronic effect of the second quaternized nitrogen.

In practice, numerous attempts[20] to isolate either (bis-NF)TEDA salts **11** or their mono-NF analogues **12** following low-temperature direct fluorination of TEDA under conditions used to procure NFQnX salts **5** failed. Hence attention was turned to the fluorination of simple mono-*N*-alkylated derivatives of TEDA ('monoquats', **13**). This simple strategy proved highly satisfactory, for not only did it provide a range of easily-isolated NFQnX analogues **9**, but also it enabled the fluorinating power to be 'tuned' through variation in the electronegativity of the quaternizing group R. Following our experience with NFQnX salts,[19] fluoride was virtually ignored as a counter-anion and attention focused initially on using the passive (non-nucleophilic, oxidation-resistant) trifluoromethanesulfonate ion (triflate, TfO^{-}) promoted and favoured by Umemoto's group during its work on the development of stable reagents (*e.g.* **4**) of the *N*-fluoropyridinium salts type (*N*-fluoropyridinium fluoride is explosive).[11]

Quite recently, through the application of new methodology developed initially for the synthesis of NFQnX salts **5c** and **5d** and involving direct fluorination of the Lewis acid adducts $Qn\cdot BF_3$ and $Qn\cdot PF_5$,[19b] highly reactive 1,4-difluoro-1,4-



1 2 3 4 X⁻ = TfO⁻, BF_4^-



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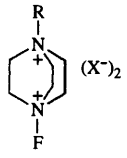
5a X⁻ = F⁻
b X⁻ = TfO⁻
c X⁻ = BF_4^-
d X⁻ = PF_6^-



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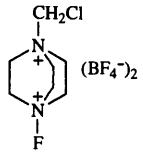
9a R = Me, $(X^-)_2$ = $(TfO^-)_2$
b R = Me, $(X^-)_2$ = $(BF_4^-)_2$
c R = Me, $(X^-)_2$ = $(PF_6^-)_2$
d R = Me, $(X^-)_2$ = (TfO⁻, BF_4^-)
e R = Me, $(X^-)_2$ = (TfO⁻, PF_6^-)
f R = Me, $(X^-)_2$ = (TfO⁻, FSO_3^-)
g R = CH_2Cl, $(X^-)_2$ = $(TfO^-)_2$
h R = CH_2Cl, $(X^-)_2$ = $(PF_6^-)_2$
i R = Et, $(X^-)_2$ = $(TfO^-)_2$
j R = CF_3CH_2, $(X^-)_2$ = $(TfO^-)_2$
k R = C_8H_{17}, $(X^-)_2$ = $(TfO^-)_2$



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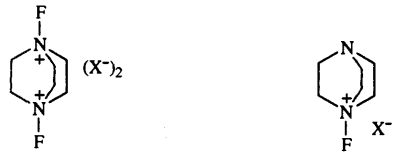
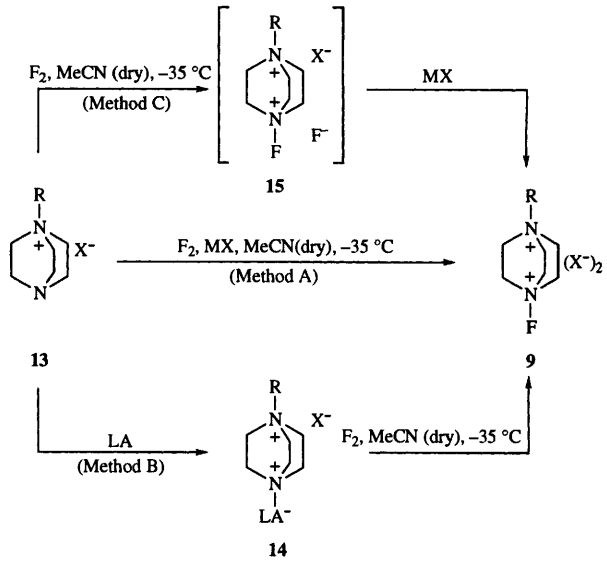


11 12

diazoniabicyclo[2.2.2]octane salts **11** have at last become available for study.[21] As described here, direct fluorination of Lewis acid (LA) adducts of TEDA monoquats **14** smoothly produces NF–TEDA reagents.

Synthesis of 1-alkyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane salts 9

Three methods for the synthesis of NF–TEDA salts **9** have been studied in detail (see Scheme 1): low-temperature (−20 to −40 °C) solution-phase (dry MeCN as solvent) fluorination [in closed *and* open systems, using, respectively, neat fluorine at low pressure (10–20 mmHg) and fluorine–nitrogen blends (normally 10% F_2 by volume, and never > 40% F_2)] of (*a*) a TEDA monoquat (**13a–c**) in the presence of an alkali-metal salt (MX) corresponding to the substrate's counter-anion (method A); of (*b*) a 1:1 TEDA–Lewis acid (LA) adduct (**14a–c**) (method B); and of (*c*) a TEDA monoquat (**13a–c**) followed by *in situ* exchange of F^- by X^- (with MX) in the 'mixed salt' **15** formed first (method C). Yields of purified products ranged from 72–97% (see Table 1), and the best routine laboratory procedure was found to be method A, used in flow-fluorination mode. This technique has been employed on several occasions to prepare 100 g batches of the 1-chloromethyl reagent **10** in 75–82% yield; on that scale, however, filtration problems associated with the removal of sodium fluoride can be a nuisance in the laboratory.

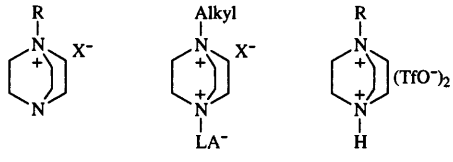


MX = $NaBF_4$, $NaPF_6$, LiOTf *etc*

LA = X^- – F^- (*e.g.* for X^- = PF_6^-, LA = PF_5)

Scheme 1 Treatment of **13** (X^- = BF_4^-) in dry MeCN at −35 °C with a 1:1 molar mixture of F_2 and BF_3 in a closed system at 10–20 mmHg has been developed as a one-step variant of Method B. However, it is not suitable for laboratory work. No 'mixed salts' (Method C) were isolated in this work. However, see ref. 15 for details of the preparation of 1-fluoro-4-methyl-1,4-diazoniabicyclo[2.2.2]octane fluoride tosylate from TEDA *via* fluorination of the corresponding monoquat tosylate **13** (R = Me, X^- = p-$MeC_6H_4SO_3^-$). A variant of Method C, not described here, is to replace MX with a Lewis acid; *e.g.* addition of BF_3 to the solution containing **15** (R = CH_2Cl, X^- = BF_4^-) gives **9** [$(X^-)_2$ = $(BF_4^-)_2$ *i.e.* **10**] in 84% yield.

The rather specialized Morton–Du Boisson closed-system fluorination technique[18] proved invaluable for carrying out small-scale exploratory work necessary to establish the feasibility of achieving safely and efficiently the synthesis of all the (new) *N*-fluoroammonium salts (**9a–k**, **10**) described here; once this had been done (including simple hazards tests on the salts, *viz.* behaviour towards thermal and mechanical shock, and exposure to bright light), attention was turned with confidence to producing the salts routinely using the relatively simple flow-fluorination method. Starting materials (**13**, **14**) were prepared in high-to-excellent yields from TEDA by methods already described.[22]



13a X⁻ = TfO⁻
b X⁻ = BF_4^-
c X⁻ = PF_6^-

14a (LA) = BF_3
b (LA) = PF_5
c (LA) = SO_3

16a R = Me
b R = CH_2Cl

Site-selective fluorination of organic substrates using NF–TEDA salts

Commercialization and the generous provision of free samples[16] of the compound now known globally as F–TEDA–BF_4 **10** has resulted in a steady stream of publications concerning application of this reagent from other research groups since our initial disclosures in this area,[1,15] and already progress has been reviewed.[23] Our pioneering contributions to knowledge of site-selective fluorination of 'model' organic substrates with NF–TEDA salts are summarized in Scheme 2. All of the reactions shown there were carried out with the 1-methyl bis(triflate) **9a**, the prototypical reagent of the Selectfluor™ class first prepared (Sharif) in 1989. For comparative purposes, fluorination of

Table 1 Summary of preparative methods used to prepare other 1-alkyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane salts, R–$^{+}$N(CH_2CH_2)$_3$N^{+}–F (X^-)$_2$ **9** (see text for R = CH_2Cl, X^- = BF_4^- **10**)

						Elemental analysis (%) Found (required)					
No.	R	X^-, Y^-	Method[a]	Yield (%)[b]	Mp/°C	C	H	BF_4	F	N	S
9a	Me	$(TfO^-)_2$	A	88	220–222	24.0 (24.3)	3.6 (3.4)		29.8 (29.95)	6.4 (6.3)	14.9 (14.4)
9b	Me	$(BF_4^-)_2$	A	84	287	26.4	4.9	54.6		8.8	
			B	97	(dec.)	(26.2)	(4.7)	(54.3)		(8.7)	
9c	Me	$(PF_6^-)_2$	A	90	182	19.0	3.4		56.7	6.1	
			B	96		(19.3)	(3.4)		(56.7)	(6.4)	
9d	Me	BF_4^- TfO^-	B	95	220 (dec.)	25.8 (25.1)	4.3 (3.9)			7.7 (7.3)	
9e	Me	PF_6^- TfO^-	B	77	204–206	21.9 (21.8)	3.2 (3.4)			6.1 (6.4)	
9f	Me	FSO_3^- TfO^-	B	72	189 (dec.)	24.8 (24.4)	3.9 (3.8)			7.4 (7.1)	
9g	CH_2Cl	$(TfO^-)_2$	A	97	165	22.2 (22.6)	3.1 (2.9)		28.0 (27.8)	5.5 (5.8)	
9h	CH_2Cl	$(PF_6^-)_2$	B	90	199 (dec.)	18.1 (17.8)	2.9 (3.0)		53.1 (52.4)	5.6 (5.9)	
9i	CH_3CH_2	$(TfO^-)_2$	A	81	216–218	26.7 (26.2)	3.5 (3.7)		28.45 (29.0)	6.4 (6.1)	
9j[c]	CF_3CH_2	$(TfO^-)_2$	A	87	208–210	23.5 (23.4)	2.6 (2.7)			5.7 (5.5)	
9k	C_8H_{17}	$(TfO^-)_2$	A	88	196–198	35.8 (35.4)	5.7 (5.4)		25.1 (24.5)	5.2 (5.2)	

[a] See Scheme 1; in method A, the following sources of the second counter-ion X^- were used: KOTf, $NaBF_4$, $NaPF_6$. [b] Pure material. [c] Recrystallization from H_2O–MeCN–Et_2O initially gave a 1 : 1 solvate of **9j** with MeCN (Found: C, 26.2; H, 2.7; F, 35.0; N, 7.4. $C_{12}H_{17}F_{10}N_3S_2O_6$ requires C, 26.0; H, 3.1; F, 34.4; N, 7.5%), the structure of which has been determined by X-ray crystallography (ref. 43). The solvent-free product **9j** was obtained by storing the solvate in a continuously evacuated tube for 3 days at room temperature.

diethyl sodio(phenyl)malonate, 1-hydroxynaphthalene and methoxybenzene was carried out with F–TEDA–BF_4 **10** and at least seven of its congeners (**9b–k**), which, like **9a**, have not been studied by other groups.

The results are summarized in Scheme 2. No persuasive evidence for a counter-anion effect was noted, in harmony with the outcome of a similar comparative study involving *N*-fluoroquinuclidinium salts,[19b] hence the tetrafluoroborate salts emerged as the most promising for commercialization from a cost-effectiveness viewpoint.

Transfer of 'F^+' from each reagent regenerates the monoquat precursors **13**, which can be recovered as proton salts **16** and recycled. For example, following electrophilic aromatic substitution of H by F in phenol using **9a** and of methoxybenzene or 2-hydroxynaphthalene by **9g**, the 1-hydro-4-alkyl salts **16a** and **16b**, respectively, can easily be recovered in at least 83% yield.

Currently there is no consensus about the mechanism of electrophilic fluorination of organic substrates with *N*-fluoro reagents,[24] and our on-going studies on the applications of F–TEDA **9** and other **1**, **5** reagents hopefully will help to resolve this situation. Our long-held view that 'F^+' transfer to electron-rich carbon sites from fluorinating agents of the N–F class needs to be viewed in terms of a substrate-dependent mechanistic continuum [$S_N2(F) \longleftrightarrow$ fully developed SET process][19a,25,26] appears to remain unchallenged.

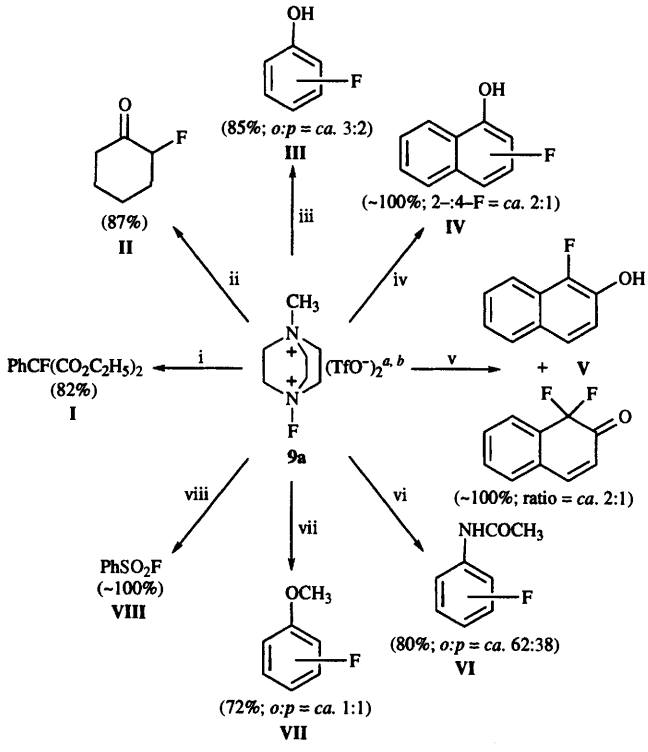
Comparison of fluorinating agents of the N–F class

Electrochemical measurements,[10] well supported by our own practical experience, indicate that the fluorinating power of F–TEDA–BF_4 **10** approaches closely that of the most active (though non-commercial) 'F^+' delivery agent of the N–F class, *N*-fluoro[bis(trifluoromethyl)sulfonyl]imide **6**.[13] Within the F–TEDA class **9**, the order of reactivity[1,10] follows the relative electron-withdrawing power of the alkylating organic group, R (CF_3CH_2 > CH_2Cl > Me ~ Et ~ C_8H_{17}), hence the 'tunability' of the series. All of these reagents are more powerful than *N*-fluoroquinuclidinium salts **5** or *N*-fluoropyridinium triflate **4** and its 2,4,6-trimethyl analogue, as nicely demonstrated by the ability of F–TEDA–BF_4 to 'transfer fluorinate' quinuclidine, pyridine and 2,4,6-trimethylpyridine at the ring nitrogen.[27]

Within the F–TEDA series, only the 2,2,2-trifluoroethyl reagent **9j** has been observed to fluorinate benzene, the slow reaction (3.5% conversion of C_6H_6 to C_6H_5F occurs in 48 h at 80 °C; reactant ratio 1 : 1) in aqueous acetonitrile (H_2O: MeCN = 1 : 4 v/v) being accelerated (20% conversion) by the addition of trifluoroacetic acid (10% by vol.). Under the same conditions (no CF_3CO_2H added), 72% conversion of the more reactive substrate methoxybenzene to a *ca.* 1 : 1 mixture of 2- and 4-fluoro(methoxy)benzene can be effected with **9j** in 5 h at 40 °C, whereas to achieve approximately the same conversion, reaction periods of 13 and 6 h, respectively, are needed with the 1-methyl (**9b**) and 1-chloromethyl (**9g**) reagents.

Overall, F–TEDA–BF_4 **10** has already proved to be one of the best general-purpose user-friendly electrophilic fluorinating agents currently available commercially. It fluorinates a wide variety of electron-rich carbon centres under mild conditions with high selectivity and often efficiency, and no special apparatus or handling techniques are required. Substrate types fluorinated so far include electron-rich alkenes,[28,29] phenylalkynes,[30] steroidal silyl enol ethers and enol acetates,[28] β-dicarbonyl compounds,[31,32] pyrimidine bases and nucleosides,[33,34] alkylbenzenes,[28] anthraquinones,[35] organometallic derivatives (Grignard reagents;[28] vinylstannanes;[36] trialkylstannylindoles;[37] cyclopentadienylthallium[38]), phosphonate esters[28] and alkyl sulfides.[28,34]

Like all the F–TEDA salts reported here, F–TEDA–BF_4 **10** is very soluble in cold water (176 g l^{-1} at 20 °C, hence providing the opportunity to carry out certain fluorinations in this medium) or dilute hydrochloric acid [note that Cl^- is not oxidized at 20 °C to chlorine, whereas Br^- and (very rapidly) I^- do give the parent elements]. It is decomposed by dilute sodium hydroxide, and reacts with cold DMSO (rapidly and exothermically) and with DMF (slowly on heating) to give as-



Scheme 2 Molar ratios of $^{+}$NF reagent:substrate close to 1:1 were employed, except where stated. Yields were not optimized; they (and, where applicable, molar ratios) were estimated by ^{19}F NMR analysis except for **I** and **II**, which are isolated yields. Yield of **I** with other $^{+}$NF reagents = 82 (**9b**), 82 (**9d**), 86 (**9e**), 73 (**9f**), 82 (**10**), 77 (**9g**), 82% (**9h**). Yield of **II** using **9b** = 88%. Yields (2-:4- ratio in parentheses) of **IV** with other reagents: 91 (61:39; **9b**), 92 (64:36; **9c**), 90 (65:35; **9d**), 92 (66:34; **9e**), 89 (60:40; **9f**), 100 (68:32; **9g**), 100 (65:35; **9h**). Yield of **V** = 83% (ratio *ca.* 2:1) with **9g**. Yield of **VI** = 80% (ratio 62:38) with **10** in boiling MeCN (15 min.). Yields of **VII** for other $^{+}$NF reagents (2-:4- ratio in parentheses) in reactions at 90 °C overnight in dry MeCN: 77 (50:50; **9c**), 75 (50:50; **9d**), 79 (55:45; **9e**), 72 (52:48; **9f**), 82 (60:40; **9g**), 76 (65:35; **9h**), 80% (67:32; **10**). *Reagents and conditions:* i, $PhC^{-}(CO_2C_2H_5)_2Na^{+}$ in THF, −10 to 20 °C; ii, 1-morpholinocyclohexene in CH_2Cl_2 at −196 to 20 °C, then aqueous 1 M HCl; iii, PhOH in CH_3OH, 20 °C; iv, 1-$HOC_{10}H_7$ (*ca.* 50% excess) in MeOH, 20 °C; v, 2-$HOC_{10}H_7$ in MeOH, −196 to 20 °C; vi, $PhCONHCH_3$ (100% excess) in MeOH; vii, $PhOCH_3$ in wet MeCN, 40 °C for 13 h; viii, $PhSO_2Na$ in MeCN at 20 °C.

yet unidentified products.[39] It is fairly soluble in acetonitrile, but only slightly so in lower alkanols or acetone. Often reactions in these solvents are aided by the addition of small quantities of water or trifluoroacetic acid (see above), which not only improves solubility but also, especially in the latter case, may impact upon the mechanism of fluorination.[39]

The results of a thorough study[16b] of the thermal behaviour of F–TEDA–BF_4 **10** prompts the warning that care should be taken not to heat bulk solid samples of any of the NF–TEDA salts reported here above 80 °C since exothermic decomposition may occur. A solution of F–TEDA–BF_4 (5.0 mmol) in boiling (82 °C) acetonitrile (50 cm^3) loses less than 10% of its 'F^{+}' transfer capability during 24 h.[40] The toxicity of F–TEDA–BF_4 is classed as moderate (male rat oral LD_{50} 640 mg kg^{-1}).[16b,23a]

Experimental

Spectroscopic analyses

IR, NMR and mass spectra were recorded using Perkin-Elmer R32 [84.6 MHz (^{19}F)], Bruker AC200 [200 MHz (^{1}H); 188.8 MHz (^{19}F); 64.2 MHz (^{11}B); 81.03 MHz (^{31}P)] and Bruker AC300 [300 MHz (^{1}H); 75.5 MHz (^{13}C)] instruments, and a Kratos MS50 (FAB) spectrometer. NMR chemical shifts were measured relative to external Me_4Si [^{1}H, ^{13}C (D_2O lock)], CF_3CO_2H (^{19}F), BF_3 (^{11}B) or H_3PO_4 (^{31}P), positive values being assigned to absorptions appearing downfield from reference signals.

Elemental analyses

Carbon, hydrogen and nitrogen contents (mass%) were determined simultaneously by combustion analysis (O_2–He mixture) using a Carlo Erba 1106 Elemental Analyser. Total fluorine was determined by tube combustion (pyrohydrolysis) of 5–20 mg samples in a stream of air and steam (silica tube at 1000 °C) followed by colorimetric measurement of fluoride ion produced (Ce–alizarin complexone). The BF_4^{-} content of water-soluble tetrafluoroborate salts was determined in aqueous solutions using suppressed (H_2SO_4) standard anion chromatography (Dionex 2010i ion-chromatograph fitted with an AG4A anion guard column as the separator column; eluent: HCO_3^{-}–CO_3^{2-}). 'Positive' fluorine content ($^{+}$N–F) was determined iodimetrically [thiosulfate titration (starch indicator) of iodine liberated by addition of an excess of potassium iodide to a solution of the compound (*ca.* 0.2 mmol) in 1:1 v/v acetone–water (10 cm^3) acidified with 10% aq HCl (2 cm^3)] or, often preferably (owing to end-point problems), using standard acid (H_2SO_4) solutions of Mohr's salt [determination ($KMnO_4$) of Fe^{3+} produced by heating (70–75 °C, 40 min) the $^{+}$NF compound (*ca.* 0.3 mmol) with acidified (H_2SO_4) aqueous 0.2 M $(NH_4)_2Fe(SO_4)_2{\cdot}6H_2O$].

Starting materials

Unless stated otherwise, starting materials were obtained from Aldrich or Fluorochem (UK), depending on availability/cost, and used as received. HPLC-Grade acetonitrile (Aldrich; H_2O < 0.02%) was employed as the solvent for fluorinations with elemental fluorine, which was generated by electrolysis of molten KF·2HF, as described previously.[18]

Fluorination techniques

Fluorinations with elemental fluorine were carried out in both 'open' (using *ca.* 1:9 v/v F_2–N_2 blends)[41] and 'closed' (neat F_2, at ≤20 mmHg pressure)[18] systems incorporating Pyrex reaction chambers, as described previously except that no cold traps were placed in the exit line when the former method was used {**CAUTION**: Owing to the high level of risk associated with work involving fluorine, only properly trained chemists should attempt to reproduce the fluorinations described here; and above all, sensible adequate prior arrangements must be made for medical treatment (HF burns).[42] Expert advice should be sought concerning the deployment of sources of fluorine [*i.e.* electrolytic generator (as used here) or cylinder of F_2–N_2 blend or neat F_2 (particularly hazardous)]. During fluorination experiments, careful control of the rate of uptake of fluorine (and hence reaction temperature) is essential to prevent the onset of potentially 'runaway' free-radical halogenation and the production of highly toxic CH_2FCN *via* hydrogen atom abstraction from the solvent (MeCN). Reaction temperatures in the range −30 to −40 °C seem to be ideal}.

Preparation of 1-alkyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]-octane salts 9

The methods developed for the synthesis of this class of compound are exemplified below. Table 1 contains details for other members (see also ref. 15). Preparative details for the immediate precursors of all the N–F salts (*i.e.* 1-alkyl-4-aza-1-azoniabicyclo[2.2.2]octane salts and their Lewis acid adducts) can be found elsewhere.[22] Spectroscopic data for compounds **9a–k** are shown in Table 2.

Table 2 NMR chemical shift (δ) and coupling constant (J/Hz) data for 1-alkyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane salts **9** in CD_3CN (unless stated otherwise) [see text for $ClCH_2$–$^+N(CH_2CH_2)_3N^+$–$F(BF_4^-)_2$ **10**]

No.	R	X^-, Y^-	δ_F	δ_H^R	$\delta_H^{2,6,7}$	$\delta_H^{3,5,8}$	δ_C^R	$\delta_C^{2,6,7}$	$\delta_C^{3,5,8}$	δ_C^X	Other
9a	Me	$(TfO^-)_2$	125.7, br s −0.1, s	3.61, s	4.60, t ($^3J_{HH}$ = $^3J_{HF}$ = 7.5)	5.10, q	54.41, m	57.82, t	58.55, d ($^2J_{CF}$ 14.7)	120.8, q (^1J 318)	
9b	Me	$(BF_4^-)_2$	125.0, br s −73.0, s	3.54, s	4.51, t ($^3J_{HH}$ = $^3J_{HF}$ = 7.5)	5.00, q	52.68, t ($^1J_{CN}$ 3.1)	56.58, t ($^1J_{CN}$ 3.0)	57.23, d ($^2J_{CF}$ 14.7)	−20.8, s	δ_B −20.8,[a] s
9c	Me	$(PF_6^-)_2$	125.3, br s 5.85, d ($^1J_{PF}$ 706)	3.40, s	4.30, t ($^3J_{HH}$ = $^3J_{HF}$ = 7.5)	4.71, q	52.45, m	56.57, m	57.33, d ($^2J_{CF}$ 14.7)		δ_p −141.2, sep ($^1J_{PF}$ 706)
9d	Me	BF_4^- TfO^-	125.8, br s −1.0, s −73.0, s	3.25, s	4.18, t ($^3J_{HH}$ = J_{HF} = 7.5)	4.65, q	52.24, m	56.56, m	57.33, d ($^2J_{CF}$ 14.7)	120.9, q ($^1J_{CF}$ 318)	δ_B −20.8, s
9e	Me	PF_6^- TfO^-	125.6, br s 5.0, d −0.8, s ($^1J_{PF}$ 696)	3.30, s	4.20, t ($^3J_{HH}$ = 7.50) ($^3J_{HF}$ = 7.60)	4.65, q	52.31, m	56.60, m	57.43, d ($^2J_{CF}$ 15.0)	121.4, q ($^1J_{CF}$ 317)	δ_p −143.2, sep. ($^1J_{PF}$ 697)
9f	Me	FSO_3^- TfO^-	124.6, br s 0.6, s −78.3	3.32, s	4.26, t ($^3J_{HH}$ = $^3J_{HF}$ = 7.5)	4.58, q	52.36, m	56.54, m	57.68, d ($^2J_{CF}$ 15.0)	120.9, q ($^1J_{CF}$ 318)	
9g	CH_2Cl	$(TfO^-)_2$	126.0, br s 0.0, s	5.62, s	4.65, t	5.10, q	70.03, m	54.77, m	58.41, d ($^2J_{CF}$ 14.9)	120.7, q ($^1J_{CF}$ 317)	
9h	CH_2Cl	$(PF_6^-)_2$	126.4, br s 6.00, d ($^1J_{PF}$ 722)	5.34, s	4.30, t ($^3J_{HH}$ = $^3J_{HF}$ = 7.5)	4.75, q	69.10, m	53.66, m	57.19, d ($^2J_{CF}$ 14.5)		δ_p −143.7, sep. ($^1J_{PF}$ 722)
9i	C_2H_5	$(TfO^-)_2$	125.0 −0.15, s	1.70, t 4.01, q	4.63, t	5.18, q					
9j[b]	CF_3CH_2	$(TfO^-)_2$	127.5, br s 16.8, t −1.6, s	5.04, q ($^3J_{HF}$ 8)	4.97, t	5.36, q					
9k	C_8H_{17}	$(TfO^-)_2$	124.0, br s −0.15, s								

[a] In D_2O. [b] In CF_3CO_2H.

Method A: Preparation of 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) 10‡ *via* fluorination of monoquat salt 13b in the presence of sodium tetrafluoroborate

(i) Flow method. A homogeneous 1:9 (v/v) mixture of F_2 (6.2 g, 16.3 mmol) and N_2 was passed at a rate of 130 cm^3 min^{-1} through a cold (−35 °C) vigorously stirred solution of 1-chloromethyl-4-aza-1-azoniabicyclo[2.2.2]octane tetrafluoroborate **13b** (R = CH_2Cl; 2.0 g, 8.0 mmol) and sodium tetrafluoroborate (0.88 g, 8.0 mmol) in dry acetonitrile (100 cm^3). The product was filtered to remove sodium fluoride, the filtrate was evaporated (Rotavapor) and the white residue was washed with AnalaR acetone and dried *in vacuo* to provide 1-*chloromethyl*-4-*fluoro*-1,4-*diazoniabicyclo*[2.2.2]*octane bis*-(*tetrafluoroborate*) **10** (2.4 g, 6.8 mmol, 84%) (Found: C, 23.8; H, 4.1; N, 7.9. $C_7H_{14}B_2ClF_9N_2$ requires C, 23.7; H, 3.9; N, 7.9%); mp (decomp.) 225 °C; $\delta_H(D_2O)$ 4.47 (t, $^3J_{HH}$ 7.50 Hz; 2,2,6,6,7,7-H), 4.90 (q, $^3J_{HF}$ 7.65 Hz; 3,3,5,5,8,8-H), 5.52 (s, CH_2Cl); $\delta_F(D_2O)$ −72.3 (s, 2 × BF_4^-), +125.6 (br s, ^+NF); $\delta_B(D_2O)$ −20.9 (br s, 2 × BF_4^-); $\delta_C(D_2O)$ 54.80 (m, C-2,-6,-7), 58.37 (d, $^3J_{CF}$ 15.17 Hz; C-3,-5,-8), 70.05 (m, CH_2Cl).

(ii) Closed system method. A cold (−35 °C) vigorously stirred solution of 1-chloromethyl-4-aza-1-azoniabicyclo[2.2.2]octane tetrafluoroborate **13b** (1.81 g, 7.28 mmol) and sodium tetrafluoroborate (0.80 g, 7.20 mmol) in dry acetonitrile (200 cm^3) was treated with neat fluorine at 10–20 mmHg pressure until uptake of the halogen became imperceptible. The product was filtered, evaporated and the residual solid washed with AnalaR acetone and dried to provide 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) **10** (2.20 g, 6.20 mmol, 85%) (Found: C, 23.6; H, 3.7; BF_4^-, 50.3; N, 7.9. Calc. for $C_7H_{14}B_2ClF_9N_2$: C, 23.7; H, 3.9; BF_4^-, 49.1; N, 7.9%), with correct NMR parameters (^1H, ^{19}F, ^{13}C).

‡ **CAUTION**: The thermal behaviour of F-TEDA-BF_4 **10** is complicated and care must be taken not to overheat neat bulk samples: exothermic decomposition can occur at temperatures > 80 °C [ref. 16(*b*)].

Method B: Preparation of 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) 10 *via* fluorination of monoquat salt–Lewis acid adduct 14a (alkyl = Me)

Fluorine diluted with nitrogen (*ca.* 10% F_2 by volume) was passed into a cold (−35 °C) vigorously stirred solution of 1-chloromethyl-4-aza-1-azoniabicyclo[2.2.2]octane trifluoromonoborane tetrafluoroborate (2.0 g, 6.3 mmol) in dry acetonitrile (150 cm^3) until the exit gas gave a strong positive test for F_2 (KI paper). The solid white residue left behind after evaporation (Rotavapor) of the reaction solution was washed with a small quantity of AnalaR acetone then dried *in vacuo* to provide spectroscopically pure (^1H, ^{19}F NMR) 1-*chloromethyl*-4-*fluoro*-1,4-*diazoniabicyclo*[2.2.2]*octane bis*(*tetrafluoroborate*) **10** (2.1 g, 5.8 mmol, 92%).

Large-scale application of method A to the preparation of 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) 10

Production of starting material. The 1-chloromethyl-4-aza-1-azoniabicyclo[2.2.2]octane chloride **13** (R = CH_2Cl, X^- = Cl^-) which formed when a solution of 1,4-diazabicyclo[2.2.2]octane (112 g, 1.00 mol) in dichloromethane (500 cm^3) was heated under reflux (2 h) was recovered by filtration (under suction, then washed with cold CH_2Cl_2 on the filter) and stored in an air-tight bottle (owing to its very hygroscopic nature); the filtrate was reheated under reflux (20 h) to provide a second crop of material. The two batches were combined and freed from dichloromethane *in vacuo* to provide 187.5 g (0.95 mmol, 95% yield) of the pure monoquat chloride,[22] mp (decomp.) 150 °C; $\delta_H(D_2O)$ 3.36 (t, $^3J_{HH}$ 7.5 Hz; 3,3,5,5,8,8-H), 3.67 (t, 2,2,6,6,7,7-H), 5.24 (s, CH_2Cl), part of which (91.9 g, 0.466 mol) was heated at 40 °C for 30 min with sodium tetrafluoroborate (51.2 g, 0.466 mol) in dry acetonitrile (1.0 l);

the mixture was then stirred at room temperature for 3 days (time not optimized), filtered under suction to remove sodium chloride, and the filtrate (plus dry MeCN used to wash the NaCl; total volume, 1.03 l) stored in an air-tight Winchester bottle to be used as a stock solution of 1-chloromethyl-4-aza-1-azoniabicyclo[2.2.2]octane tetrafluoroborate needed for fluorination experiments; the yield of this monoquat tetrafluoroborate **13b** (R = CH_2Cl) was 95%, as determined by evaporation of a 50 cm^3 portion to give analytically pure material (Found: C, 33.6; H, 5.9; BF_4^-, 34.9; N, 11.2. Calc. for $C_7H_{14}ClN_2^+$-BF_4^-: C, 33.8; H, 5.6; BF_4^-, 34.9; N, 11.3%); mp 123–125 °C; $\delta_H(D_2O)$ 3.35 (t, $^3J_{HH}$ 7.5 Hz; 6 H), 3.65 (t, 6 H), 5.20 (s, 2 H).

Fluorination stage. Fluorine (18.5 g, 0.49 mol) diluted with nitrogen ($1F_2$:$9N_2$ by volume) was passed over 5 h into a cold (−40 °C) stirred mixture of sodium tetrafluoroborate (43.9 g, 0.40 mol) in 480 cm^3 of dry acetonitrile and 920 cm^3 of the stock solution of 1-chloromethyl-4-aza-1-azoniabicyclo[2.2.2]octane tetrafluoroborate **13b** (R = CH_2Cl, 99.4 g, 0.40 mol). When the exit gas gave a strong positive test (KI) for fluorine, the product was purged with nitrogen (120 cm^3 min^{-1}) for 1 h (at 20 °C, to ensure no fluorine remained), diluted with dry acetonitrile (400 cm^3, to ensure that none of the required product had precipitated with the sodium fluoride produced), stored overnight (to allow the finely-divided sodium fluoride to settle), then filtered (through a 5 cm bed of Celite, which proved far more convenient and efficient than filter paper) and the filtrate worked-up in standard fashion (3-crop evaporation technique) to provide 95% pure (by ^1H and ^{19}F NMR) 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) **10** (116.7 g; corrected yield 0.31 mol, 77.5%), the contaminants being starting material (< 1% recovery) and a hydrofluoride salt of the starting monoquat salt. This material was of quite adequate purity for use in preparative electrophilic fluorination experiments.

Fluorination of organic substrates with 1-alkyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane salts 9 and 10

Diethyl phenylmalonate. The technique used previously[18] during work on *N*-fluoroquinuclidinium salts was employed except that the fluorinating agent (0.85 mmol) was dissolved in cold (−10 °C) acetonitrile (30 cm^3) and the THF solution (15 cm^3) of diethyl sodio(phenyl)malonate [from NaH and 0.85 mmol of $PhCH(CO_2C_2H_5)_2$] was cooled to −10 °C before it was added to the reagent; as soon as mixing had occurred, the cooling bath was removed and when the reaction mixture had warmed to room temperature it was diluted with diethyl ether (50 cm^3) and worked up. The diethyl fluoro(phenyl)malonate isolated was identified by ^1H and ^{19}F NMR spectroscopy [yields: 82 (**9a**), 82 (**9b**), 82 (**9d**), 86 (**9e**), 73 (**9f**), 82 (**10**), 77 (**9g**) and 82% (**9h**)].

1-Morpholinocyclohexene. Using exactly the same method described previously for *N*-fluoroquinuclidinium fluoride,[18] 1-fluoro-4-methyl-1,4-diazoniabicyclo[2.2.2]octane ditriflate **9a** (0.26 g, 0.55 mmol) was used to fluorinate 1-morpholinocyclohexene (0.10 g, 0.59 mmol) in dichloromethane at 20 °C, to give, following an acidic (aq. HCl) work-up of the initial product and a standard extraction procedure, 2-fluorocyclohexanone (0.60 g, 0.52 mmol, 87%), identified by IR and NMR spectroscopy. Virtually the same yield (88%) of 2-fluorocyclohexanone was obtained when 1-fluoro-4-methyl-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) **9b** was used as the fluorinating agent on the same scale.

Sodium benzenesulfinate. The experiment performed previously[19a] in a 5 mm i.d. NMR tube with *N*-fluoroquinuclidinium triflate was repeated using 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) **10** (0.10 g, 0.28 mmol) and dry sodium benzenesulfinate (0.09 g, 0.28 mmol) in dry acetonitrile (2 cm^3). A reaction occurred immediately, giving benzenesulfonyl fluoride [δ_F 142.5 (SO_2F)] in quantitative yield (estimated by NMR analysis, using the ^{19}F signal of BF_4^- as the internal standard).

Phenol. 1-Fluoro-4-methyl-1,4-diazoniabicyclo[2.2.2]octane ditriflate **9a** (0.81 g, 1.82 mmol) was added to a stirred solution of phenol (0.17 g, 1.81 mmol) in dry methanol (10 cm^3). Although a reaction appeared to occur immediately (the solution became light yellow), the mixture was stirred overnight then diluted with dichloromethane (50 cm^3), causing 4-methyl-1,4-diazoniabicyclo[2.2.2]octane ditriflate **16a** (0.65 g, 1.52 mmol, 84%), mp 213–215 °C, to precipitate. This byproduct was recovered by filtration, dried *in vacuo* and identified by comparison of its ^1H and ^{19}F NMR spectra with those of a pure sample (Found: C, 25.3; H, 3.6; F, 26.5; N, 6.7. $C_9H_{16}F_6N_2O_6S_2$ requires C, 25.3; H, 3.7; F, 26.8; N, 6.6%); $\delta_H[(CD_3)_2CO]$ 4.40 (s, CH_3), 5.20 (m, 2,2,6,6,7,7-H), 5.30 (m, 3,3,5,5,8,8-H), 5.80 (br s, ^+NH); $\delta_F[(CD_3)_2CO]$ −0.3 (s); mp 213–215 °C, prepared from 1-methyl-4-aza-1-azoniabicyclo-[2.2.2]octane triflate and triflic acid. The filtrate was evaporated (Rotavapor) and the residue shown by NMR analysis to be a *ca.* 3:2 mixture of 2- and 4-fluorophenol (0.17 g, 1.52 mmol, 85%).

1-Hydroxynaphthalene. 1-Fluoro-4-methyl-1,4-diazonia-[2.2.2]octane ditriflate **9a** (0.10 g, 0.22 mmol) was added to a stirred solution of 1-hydroxynaphthalene (0.05 g, 0.35 mmol) in dry methanol (2 cm^3). After 1 h, NMR analysis (^1H, ^{19}F) of the reaction mixture revealed that the N–F reagent had been completely converted to its ^+NH analogue with the formation of a *ca.* 2:1 mixture of 2- and 4-fluoro-1-hydroxynaphthalene in 100% yield (determined using the $CF_3SO_3^-$ signal as an internal standard).

In a series of comparative reactions, a degassed solution (prepared cryogenically: 3 freeze–pump–thaw cycles, from −196 °C) of each of the salts **9b–h** and **10** (0.42–0.68 mmol) and a small excess of 1-hydroxynaphthalene (0.49–0.69 mmol) in dry methanol (20 cm^3) contained in an evacuated Rotaflo tube (*ca.* 100 cm^3) was stirred magnetically overnight (a quite excessive time) at room temperature after the tube had warmed up from −196 °C. Each product was diluted with diethyl ether (50 cm^3) and the mixtures washed with 0.5 M oxalic acid (20 cm^3), 10% aqueous potassium hydrogen carbonate (20 cm^3) and saturated brine (20 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure. Residues were analysed by NMR and found to comprise mixtures of 2- and 4-fluoro-1-hydroxynaphthalene with the following compositions [yields in %, determined using hexafluorobenzene (0.01 g, 0.05 mmol) as internal standard, and reagent code number are given in parentheses]: 61:39 (91; **9b**); 64:36 (92; **9c**); 65:35 (90; **9d**); 66:34 (92; **9e**); 60:40 (89; **9f**); 68:32 (100; **10**); 68:32 (100; **9g**); 65:35 (100%; **9h**).

2-Hydroxynaphthalene. 1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane di-triflate **9g** (0.75 g, 1.57 mmol) was added to a solution of 2-hydroxynaphthalene (0.23 g, 1.57 mmol) in dry methanol (10 cm^3) contained in a Rotaflo tube (*ca.* 100 cm^3) equipped with a magnetic stirrer follower. A reaction appeared to take place immediately, producing a white solid, suspended in a yellow liquid; however, the mixture was frozen (−196 °C) and degassed (3 freeze–pump–thaw cycles) before the tube was sealed, allowed to warm to room temperature and its contents stirred for 30 min. The white solid present was recovered by filtration, recrystallized from acetone and found to be 1-chloromethyl-1,4-diazoniabicyclo[2.2.2]octane ditriflate **16b** (0.60 g, 1.30 mmol, 83%) (Found: C, 23.4; H, 3.2; Cl, 7.6; N, 5.8. $C_7H_{15}F_6N_2O_6S_2$ requires C, 23.4; H, 3.2; Cl, 7.7; N, 6.1%); mp (decomp.) 200 °C; $\delta_H(D_2O)$ 3.97 (m, 3,3,5,5,8,8-H), 4.16 (m, 2,2,6,6,7,7-H), 5.50 (s, CH_2Cl); δ_C 44.90 (s, C-3,5,8), 51.32 (s, C-2,6,7), 70.02 (s, CH_2Cl), 122.2 (q, $^1J_{CF}$ 318 Hz; $CF_3SO_3^-$); δ_F −1.0 ($CF_3SO_3^-$). The filtrate was evaporated under reduced pressure, and the residue was shown by ^{19}F NMR spectroscopy to contain 1-fluoro-2-hydroxynaph-

thalene and 1,1-difluoro-2-oxo-1,2-dihydronaphthalene in a molar ratio of *ca.* 2:1. An almost identical result was achieved using reagent **9a** on the same scale and under the same conditions.

Acetanilide. A mixture of 1-fluoro-4-methyl-1,4-diazoniabicyclo[2.2.2]octane ditriflate **9a** (0.10 g, 0.22 mmol), acetanilide (0.06 g, 0.45 mmol) and dry methanol (2 cm^3) was heated in a water bath (70 °C) until a clear solution was obtained (4 min), cooled, analysed by ^{19}F NMR spectroscopy and found to contain 2- and 4-fluoroacetanilide (molar ratio 62:38; total yield 80%, determined using the $CF_3SO_3^-$ signal as an internal reference). Use of reagent **10** (0.21 mmol) instead of **9a** in boiling MeCN (2 cm^3) for 15 min gave virtually the same result.

Methoxybenzene. A magnetically-stirred degassed solution of 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane ditriflate **9g** (0.51 g, 1.06 mmol) and methoxybenzene (0.115 g, 1.06 mmol) in dry acetonitrile was heated at 90 °C overnight in an evacuated sealed tube (Rotaflo; *ca.* 100 cm^3). The clear reaction solution was diluted with dry diethyl ether (30 cm^3) and the 1-chloromethyl-4-hydro-1,4-diazoniabicyclo[2.2.2]octane ditriflate **16b** (0.40 g, 0.87 mmol, 82%; identified by ^1H and ^{19}F NMR) which precipitated was removed by filtration; evaporation of the filtrate at reduced pressure (Rotavapor) gave a mixture (0.11 g, 0.87 mmol, 82%) which was shown by ^{19}F NMR analysis to comprise 2-fluoromethoxybenzene (60%) and 4-fluoromethoxybenzene (40%).

In a comparative study, each of the ^+NF salts **9b–h** and **10** (1.06–1.56 mmol) was used to fluorinate an equimolar proportion of methoxybenzene in dry acetonitrile at 90 °C overnight under anaerobic conditions, exactly as described above. The mixtures of 2- and 4-fluoromethoxybenzene recovered were analysed by GLC (2 m silicone at 160 °C) and ^{19}F NMR spectroscopy (C_6F_6 internal standard). Product ratios (2-FC_6H_4OMe: 4-FC_6H_4OMe) and total yields (%) were as follows: (**9b**) 50:50, 77; (**9c**) 50:50, 75; (**9d**) 57:43, 79; (**9e**) 55:45, 79; (**9f**) 52:48, 72; (**9g**) 60:40, 82; (**9h**) 65:35, 76; (**10**) 67:32, 80%.

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