N,*N*′-Difluoro-1,4-diazoniabicyclo[2.2.2]octane Salts, Highly Reactive and Easy-to-Handle Electrophilic Fluorinating Agents[1)]

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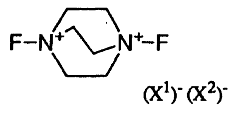
A series of *N*,*N*′-difluoro-1,4-diazoniabicyclo[2.2.2]octane salts were synthesized in a pure form by the fluorination of 1,4-diazabicyclo[2.2.2]octane with F_2 diluted with N_2 in the presence of a Brønsted acid in fluoro alcohol or acetonitrile or by fluorination followed by a treatment with a different Brønsted or Lewis acid. Their complete structural assignment was made based on spectral and elemental analyses of the isolated crystals. A great through-bond interaction between the two N–F's of the salt was observed on ^{19}F NMR. An assessment was made of the usefulness of *N*,*N*′-difluoro-1,4-diazoniabicyclo[2.2.2]octane bis(triflate), bis(HSO_4), bis(BF_4), and bis(SbF_6) salts for electrophilic fluorination; the bis(BF_4) salt was demonstrated to be widely applicable as a highly reactive and easy-to-handle fluorinating agent. Thus, the bis(BF_4) salt readily fluorinated activated aromatics, active methylene compounds or their salts, substituted styrenes, and vinyl acetates under mild conditions. It was shown that one N–F of the salt was effective for fluorination and that the other N–F played a role to activate fluorination through the bonds. Thus, the reaction mechanism was discussed, and fluorination followed by an immediate intramolecular one-electron transfer was suggested.

Since fluorine-containing compounds have some characteristic physical, chemical, or biochemical properties due to the highest electronegativity, low polarizability, and small size of the fluorine element, many investigations have been actively made to develop fluorinated compounds useful as medicines, agricultural chemicals or new materials.[2)] Accordingly, a method for selective and easy fluorination has become increasingly important. Many *N*-fluoro compounds have been developed as easy-to-handle electrophilic fluorinating agents,[3)] which include *N*-fluorosulfonamides,[4)] *N*-fluoropyridinium salts,[5)] *N*-fluoroquinuclidinium salts,[6)] *N*-fluorobis(perfluoroalkylsulfonyl)imides,[7)] *N*-fluorodisulfonimides,[8)] *N*-alkyl-*N*′-fluoro-1,4-diazoniabicyclo[2.2.2]octane salts,[9)] *N*-fluoro-*N*′-hydroxy-1,4-diazoniabicyclo[2.2.2]octane salts,[10)] and *N*-fluoro oxathiazine dioxides.[11)] However, more reactive and easy-to-handle fluorinating agents have been needed to make the fluorination scope broad.

N,*N*′-Difluoro-1,4-diazoniabicyclo[2.2.2]octane salts **1**,[9a)] a new type of compounds having two cationic N–F moieties in a molecule, may be expected to be stable crystals and to act as highly reactive multi-fluorinating agents, since salts **1** have a highly symmetric salt structure and the two strongly electronegative N–F's may activate each other through their bonds. A report by Banks et al. described how attempts to synthesize salts **1** proved to be unsatisfactory.[9a)] Although their quite recent communication reported on the synthesis, the reported salts **1** were moisture-sensitive and data other than the NMR data were not reported.[12)]

Independently, we synthesized a series of salts **1a**—**f** in pure form (Fig. 1), and developed them as useful fluorinating agents. The salts **1a** and **1d**—**f** obtained by us were nonhygroscopic and stable crystals. In this paper we describe useful synthetic methods for pure salts **1**, the complete structural assignment of salts **1**, their usefulness as electrophilic fluorinating agents, and their fluorination mechanism.



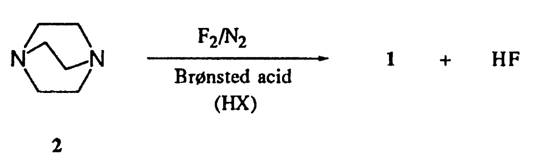
1a; $X^1=X^2=OSO_2CF_3$
1b; $X^1=X^2=HSO_4$
1c; $X^1=HSO_4$, $X^2=F(HF)_2$
1d; $X^1=X^2=BF_4$
1e; $X^1=X^2=SbF_6$
1f; $X^1=X^2=PF_6$

Fig. 1.

Results and Discussion

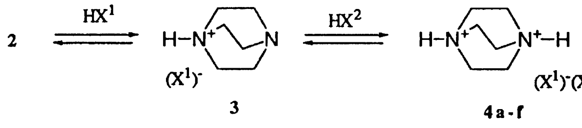
Synthesis of *N*,*N*′-Difluoro-1,4-diazoniabicyclo[2.2.2]octane Salts 1a— f. According to Banks's report, *N*,*N*′-difluoro-1,4-diazoniabicyclo[2.2.2]octane difluoride, or bis(triflate) (**1a**) (Fig. 1), could not be obtained by the fluorination of 1,4-diazabicyclo[2.2.2]octane (**2**) with neat fluorine at ca. 20 mmHg pressure (1 mmHg = 133.322 Pa) or fluorine diluted with nitrogen in the presence or absence of lithium triflate.[9a)] Their quite recent communication described how salts **1a** and **1d**—**f** could be synthesized by the fluorination of complexes of **2** with 2 equimolar amounts of Lewis acid, the fluorination of complexes of **2** with one equimolar Lewis acid in the presence of sodium tetrafluoroborate, the fluorination of *N*,*N*′-bis(trimethylsilyl)-1,4-diazoniabicyclo[2.2.2]octane bis(triflate), or the fluorination of *N*-(heptafluorobutyryl)-1,4-diazoniabicyclo[2.2.2]octanetrifluoromonoborane tetrafluoroborate.[12)] However, the yields were not reported at all.[12)]

Independently, we found that a series of salts **1a**—**f** could be easily produced in high yields by the fluorination of **2** with 10% F_2/N_2 in 1,1,1,3,3,3-hexafluoro-2-propanol or acetonitrile in the presence of 2 or less equimolar amounts of a Brønsted acid, as shown in Eq. 1 and Table 1.



(1)

The fluorination yields were sensitive to the amount of the Brønsted acid used, as shown in Table 1. Thus, when 2 or less equimolar amounts of triflic acid to **2** was used, bis(triflate) **1a** was produced in high yields (Runs 2 and 3); however, with 2.1 or more equimolar amounts of triflic acid brought about a great decrease in the yields of **1a**, leaving a large amount of the unreacted proton salt **4a** (Run 4). This appeared to be attributed to a great decrease in the fluorination rate caused by an excess of the acid used. As shown in Eq. 2, there exists an equilibrium between mono-proton salt **3** and bis-proton salt **4**. Excess of an acid formed proton salt **4** along with the disappearance of **3**, which may have been reactive to F_2. Since this should greatly decrease the fluorination rates, the fluorination yields decrease.



(2)

With sulfuric acid, a similar fluorination of **2** occurred. With 1.99 equimolar amounts of sulfuric acid, bis(HSO_4) **1b** was obtained in 87% yield (Run 5). With one equimolar amount of sulfuric acid, HSO_4–$F(HF)_2$ salt **1c** was isolated in 85% yield (Run 6). The number of HF of **1c** was determined by an elemental analysis. From a comparison with Runs 1 and 5, the fluorination efficiency with sulfuric acid was much higher than that with triflic acid, since even a smaller amount of F_2 provided a high yield of **1b**, and no proton salt **4b** (Run 5).

With 1.95 and 2.0 equimolar amounts of HBF_4 (Runs 7 and 8), the fluorination of **2** in 1,1,1,3,3,3-hexafluoro-2-propanol solvent resulted in a 77:23 and 76:24 mixture of **1d** and **4d**. However, similar fluorination in acetonitrile solvent gave a 2:74 mixture of **1d** and **4d** (Run 9). Thus, most of the proton salt **4d** remained unreacted in the latter case. Any attempts to isolate pure salt **1d** from mixtures of **1d** and **4d** by recrystallization or by further fluorination failed, probably due to the very low solubility and mixed crystals of **1d** and **4d**. In contrast, with $HSbF_6$ and HPF_6, **2** was smoothly fluorinated in acetonitrile to give pure, or almost pure, salts **1e** and **1f** in good or high yields (Runs 10—12). This may have been due to the high solubility of **4e** and **4f** in acetonitrile.

Counteranion Replacement Reaction. We found that when salt **1** was treated with a Brønsted acid, which was different from the conjugated acid of the counteranion of **1**, a counteranion replacement reaction occurred to give salt **1′** having a different counteranion (Eq. 3). The results are shown in Table 2. Salts **1a**, **1b**, **1c**, and **1e** were treated with an excess amount of HBF_4 in acetonitrile or 1,1,1,3,3,3-hexafluoro-2-propanol to give pure bis(BF_4) **1d** as white precipitates in 79, 82, 100, and 97% yields, respectively (Runs 1—4). Since the crystals obtained by filtration were pure, further purification was unnecessary. Thus, this counteranion replacement was the only method to obtain pure bis(BF_4) **1d**. A similar treatment of **1a** with $HSbF_6$ and HPF_6 gave pure **1e** and highly pure **1f** (purity 92%) in 81 and 79% yields, respectively (Runs 5 and 6). The driving force for the replacement reaction may have been due to the difference in the solubility between the starting salt and the product salt, because **1a** having relatively good solubility, could not be obtained in a pure form from **1c**.

Table 1. Direct Fluorination of **2** in the Presence of a Brønsted Acid

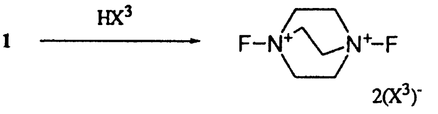
Run	**2** (mmol)	Solvent (ml)	Concentration	Acid	Molar ratio	T[a)]	Products (Yield/%)[b)]
			of **2** (mol dm^{-3})		Acid/**2**/F_2	°C	
1	2.3	$(CF_3)_2CHOH$ (5)	0.46	TfOH	1.95/1/6	0	**1a** (68), **4a** (32)
2	3.0	$(CF_3)_2CHOH$ (6)	0.5	TfOH	1.95/1/12	0	**1a** (100)
3	3.0[c)]	$(CF_3)_2CHOH$ (6)	0.5	TfOH	2 : 1 salt(**4a**)/12	0	**1a** (95), **4a** (2)
4	3.0	$(CF_3)_2CHOH$ (3.5)	0.5	TfOH	2.1/1/12	0	**1a** (18), **4a** (82)
5	10.0	$(CF_3)_2CHOH$ (40)	0.25	H_2SO_4	1.99/1/5	−5	**1b** (87)
6	3.0	$(CF_3)_2CHOH$ (12)	0.25	H_2SO_4	1.0/1/6	−5	**1c** (85)
7	3.0	$(CF_3)_2CHOH$ (30)	0.1	HBF_4[d)]	1.95/1/1 2	0	**1d** (77), **4d** (23)
8	1.9[c)]	$(CF_3)_2CHOH$ (19)	0.1	HBF_4	2 : 1 salt(**4d**)/6	0	**1d** (76), **4d** (24)
9	3.0[c)]	CH_3CN (12)	0.25	HBF_4	2 : 1 salt(**4d**)/6	−30	**1d** (2), **4d** (74)
10	3.0	CH_3CN (12)	0.25	$HSbF_6$[e)]	1.95/1/6	−30	**1e** (56)
11	3.0[c)]	CH_3CN (12)	0.25	$HSbF_6$	2 : 1 salt(**4e**)/6	−30	**1e** (70), **4e**(5)
12	3.0[c)]	CH_3CN (12)	0.25	HPF_6	2 : 1 salt(**4f**)/6	−30	**1f** (81)

a) Bath temperature. b) Isolated yield. c) In this experiment, proton salt **4a**, **4d**, **4e**, or **4f** (acid/**2** = 2/1) was used, which was prepared from **2** and an excess amount of a Brønsted acid in a separate experiment (see Materials of Experiment section). d) A 85% HBF_4/diethyl ether solution was used. e) $HSbF_6 \cdot 6H_2O$ was used.

Table 2. Counteranion Replacement Reaction

Run	Starting salt (mmol)	Solvent (ml)	Acid	(mmol)	Conditions	Product	(Yield/%)[a]
1	**1a** (12)	$(CF_3)_2CHOH$ (50)	HBF_4	(39.6)[b]	r.t., 20 min	**1d**	(79)
2	**1b** (2.0)	CH_3CN (4)	HBF_4	(6.6)[b]	r.t., 15 min	**1d**	(82)
3	**1c** (0.8)	$(CF_3)_2CHOH$ (4)	HBF_4	(3.5)[b]	r.t., 1 h	**1d**	(100)
4	**1e** (2.1)	CH_3CN (8)	HBF_4	(6.8)[b]	r.t., 15 min	**1d**	(97)
5	**1a** (1.6)	$(CF_3)_2CHOH$ (5)	$HSbF_6$	(3.4)[c]	r.t., 15 min	**1e**	(81)
6	**1a** (1.5)	$(CF_3)_2CHOH$ (5)	HPF_6	(3.2)[d]	r.t., 15 min	**1f**	(79)[e]

a) Isolated yield of pure **1** except for Run 6. b) A 85% HBF_4/diethyl ether solution was used. c) $HSbF_6\cdot 6H_2O$ was used. d) A 60% HPF_6 aq solution was used. e) Purity of **1f** was 92%.



1' (3)

Fluorination and Successive Counteranion Replacement Reaction. A one-pot reaction consisting of the direct fluorination of **2** in the presence of sulfuric acid and a successive treatment with a different Brønsted acid or Lewis acid should thus be an effective method to prepare very insoluble salts, such as bis(BF_4) **1d**, since **1d** could not be synthesized in a pure form by direct fluorination alone (as mentioned above) (Eq. 4).

$$2 \xrightarrow[\substack{\text{1) } F_2/N_2 \text{ - } H_2SO_4 \\ \text{2) Brønsted or Lewis acid}}]{\text{One-pot reaction}} 1 \qquad (4)$$

As shown in Table 3, the fluorination of **2** in the presence of an equimolar amount of sulfuric acid in acetonitrile or a fluoro alcohol, and a successive treatment with HBF_4 or $Et_2O\cdot BF_3$, gave high yields of pure, or almost pure, **1d**.

In acetonitrile, one equimolar amount of sulfuric acid gave a 65% yield of **1d** (Run 3); the yields increased with increasing the amounts of sulfuric acid (Runs 4—7). This suggested that the excess acid restrained the fluoride anion (F^-)-induced decomposition of the *N,N'*-difluoro-1,4-diazoniabicyclo[2.2.2]octane salt structure by protonation to F^-, which resulted from fluorination. This may be supported by the fact that the use of acidic 1,1,1,3,3,3-hexafluoro-2-propanol or 2,2,2-trifluoroethanol as a solvent afforded high yields of product **1d**, even with one equimolar amount of sulfuric acid (Runs 1 and 2). However, with 2.0 equimolar amounts of sulfuric acid, the yield was slightly reduced (Run 8). This may be attributed to the slow fluorination rate due to a decrease in the concentration of the reactive mono-proton salt **3b**.

This one-pot reaction was also useful for the synthesis of bis(SbF_6) **1e** and bis(PF_6) **1f**. Thus, the fluorination of **2** with one equimolar amount of sulfuric acid in 1,1,1,3,3,3-hexafluoro-2-propanol, followed by a treatment with SbF_5 and PF_5, produced pure **1e** and **1f** in high yields, respectively (Runs 9 and 10).

Structural Assignment of *N,N'*-Difluoro-1,4-diazoniabicyclo[2.2.2]octane Salts 1a—f. A structural assignment of salts **1a**—**f** was carried out by spectral and elemental analyses. Thus, ^{19}F NMR showed a broad singlet peak at around 40 ppm, corresponding to the cationic N–F fluorine atoms. ^1H NMR showed a broad doublet–doublet with coupling constants of 3.5 and 3.5 Hz around 5.0 ppm, which corresponds to the CH_2 protons. Since the doublet–doublet

Table 3. One-Pot Synthesis of *N,N'*-Difluoro-1,4-diazoniabicyclo[2.2.2]octane Salts

Run[a]	Molar ratio H_2SO_4/**2** (3 mmol)	Solvent (12 mml)	T °C[b]	Acid	(mmol)	T °C[c]	Product	Yield (%)[d]
1	1.0/1	$(CF_3)_2CHOH$	−5	HBF_4	(10.3)[e]	r.t.	**1d**	81
2	1.0/1	CF_3CH_2OH	−30	HBF_4	(10.3)[e]	r.t.	**1d**	83
3	1.0/1	CH_3CN	−20	BF_3	(6.3)[g]	−20→r.t.	**1d**	65
4	1.1/1	CH_3CN	−20	BF_3	(6.3)[g]	−20→r.t.	**1d**	77[f]
5	1.3/1	CH_3CN	−20	BF_3	(6.3)[g]	−20→r.t.	**1d**	83
6	1.5/1	CH_3CN	−20	BF_3	(6.3)[g]	−20→r.t.	**1d**	88
7	1.7/1	CH_3CN	−20	BF_3	(6.3)[g]	−20→r.t.	**1d**	87
8	2.0/1	CH_3CN	−20	BF_3	(6.3)[g]	−20→r.t.	**1d**	81
9	1.0/1	$(CF_3)_2CHOH$	−5	SbF_5	(6.6)	r.t.	**1e**	87
10	1.0/1	$(CF_3)_2CHOH$	−5	PF_5	(187)[h]	r.t.	**1f**	88

a) The reactions were carried out in a solvent (12 ml) using **2** (3 mmol) and 10% F_2–90% N_2 (F_2: 18mmol). b) Bath temperature for the fluorination reaction. c) Bath temperature for the counteranion replacement reaction. d) Isolated yields of pure **1** except for Run 4. e) A 85% HBF_4/diethyl ether solution was used. f) Purity of **1d** was 98% and the remaining 2% was **4d**. g) $Et_2O\cdot BF_3$ was used. h) Gaseous PF_5 was introduced into the reaction mixture.

of the proton changed to a singlet upon irradiating the N–F fluorine signal, the CH_2 protons coupled with two N–F fluorine atoms. The presence of two fluorine atoms in salts **1a**—**f** was further supported by the fact that there is a doublet–doublet with coupling constants of 11.7 and 11.7 Hz at 61.1 ppm in ^{13}C NMR of **1a**, which couples with the two N–F fluorine atoms. Salts **1a**, **1d**, **1e**, and **1f** are nonhygroscopic and stable crystals and bis(HSO_4) **1b** and HSO_4–F$(HF)_2$ **1c** are hygroscopic crystals. Elemental analyses of all salts **1a**—**f** are in good agreement with the assigned formula. The number of HF in salt **1c** was determined by the observed elemental-analysis value (27.9(±1.0)%) for fluorine, which agreed with the calulated value of 28.08%.

As mentioned above, we succeeded in synthesizing a series of *N,N′*-difluoro-1,4-diazoniabicyclo[2.2.2]octane salts in pure form. This may suggest that salts **1a**, **1d**, **1e**, and **1f**, which were isolated by Banks et al., should be impure, because all of their products were moisture-sensitive.[12)] Their assignment of the structure to the *N,N′*-difluoro-1,4-diazoniabicyclo[2.2.2]octane salts rested on the NMR data.[12)]

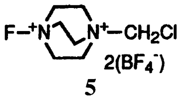
At first, it appeared strange that the N–F fluorine chemical shifts of salts **1a**—**f** appeared at higher magnetic field, by as much as ca. 9 ppm, than those (around 49 ppm) of *N*-chloromethyl-*N′*-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (**5**),[9a)] because salts **1** have a higher reactivity than does **5** (as will be mentioned later). Since the reactivity of N–F compounds essentially depends on the electron deficiency at the fluorine,[5d,5g)] the N–F fluorine chemical shifts of **1** was expected to appear at lower fields than that of **5**. This unexpected upfield shift may indicate that the fluorine atoms have an electron density increased by the through-bond interaction between the two N–F's. In contrast with the fluorine, the CH_2 proton chemical shift (5.0 ppm) of **1** showed the expected downfield shift compared with those (4.76 and 4.31 ppm in CD_3CN) of **5**.

The through-bond upfield shift of the fluorine may be supported by the fact that the ^{19}F chemical shift of *p*-difluorobenzene appears at −119.8 ppm (in CD_3CN), which is at a higher field by 6.2 ppm than that (−113.6 ppm) of fluorobenzene, due to the interaction between the two fluorine atoms in the *para*-position through the bonds. The great through-bond interaction between the two nitrogens in the 1,4-diazabicyclo[2.2.2]octane system has been noticed and estimated by calculations.[13)] Thus, the ^{19}F NMR spectra of salts **1a**—**f** have made possible a direct observation of the through-bond interaction in the ground state.

Electrophilic Fluorination with *N,N′*-Difluoro-1,4-diazoniabicyclo[2.2.2]octane Salts. When bis(triflate) **1a** was allowed to react with an equimolar amount of anisole in formic acid at room temperature, fluorination readily occurred to give *o*- and *p*-fluoroanisole and 2,4-difluoroanisole in 21, 24, and 4% yields, based on the amount of anisole used, respectively, as shown in Table 4 (Run 1). Similar results were obtained with **1b**, **1d**, and **1e** (Runs 2—4). All of the fluorinations were completed within 15 min. A purple color appeared at the beginning of the fluorination, and then the solution became pale brown and homogeneous. As a comparison, the fluorination with related salt **5** was very slow under the same conditions, although **5** was more soluble in formic acid than was *N,N′*-difluoro bis(BF_4) **1d**. The total fluorinated products were only 5% yield, and 81% of anisole remained unreacted (Run 5). Thus, as expected, salts **1** having two N–F's, were much more powerful than **5**, having an N–F and N–CH_2Cl moiety. This clearly indicated that the N–F moiety activated the other N–F more than did N–CH_2Cl, due to the highest electronegativity of fluorine. As discussed above, the ^{19}F NMR analysis suggested that the N–F fluorine atoms of **1** have their electron density increased due to the through-bond interaction, compared to the N–F fluorine atom of **5**. However, the electron density at the nitrogen atoms or the 1,4-diazabicyclo[2.2.2]octane nucleus of **1** should be lower than at those of **5** due to the higher electoronegativity of fluorine than that of CH_2Cl. The fluorinating power should thus depend on the electron density at the nitrogen atoms or the bicyclo[2.2.2]octane nucleus rather than that at the fluorine atoms.

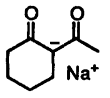
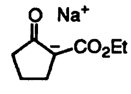
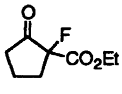
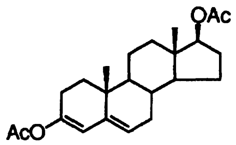
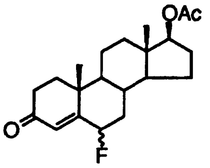
Fluorination of Various Nucleophiles with *N,N′*-Difluoro-1,4-diazoniabicyclo[2.2.2]octane Salts. Since bis(BF_4) salt **1d** is the most economical fluorinating agent in this series, the fluorination of various nucleophiles was examined mainly using **1d**. As shown in Table 5, salt **1d** has been found to be a widely applicable fluorinating agent.

Table 4. Fluorination of Anisole with *N,N′*-Difluoro-1,4-diazoniabicyclo[2.2.2]octane Salts and Related Salt **5**

Run[a)]	Salt	Conversion of anisole (%)	Yield (%)[b)]		
			o-Fluoroanisole	*p*-Fluoroanisole	2,4-Difluoroanisole
1	**1a**	100	21	24	4
2	**1b**	92	33	29	4
3	**1d**	100	30	29	5
4	**1e**	100	22	23	5
5	 **5**	19	3	2	0

a) The reactions were carried out in HCOOH (2 ml) using 1 mmol of anisole and 1 mmol of salt **1a**, **1b**, **1d**, **1e**, or **5** at room temperature for 15 min. b) Yields were calculated on the basis of anisole used.

Table 5. Fluorination of Various Nucleophiles with **1**

Run[a]	Nucleophiles	1	Solvent	Conditions	Fluorinated products	Yield (%)[b]
1	Phenol	**1d**	HCOOH	r.t., 15 min	*o*-Fluorophenol *p*-Fluorophenol 2,4-Difluorophenol	29 12 7
2	Anisole	**1e**	CH_3CN	r.t., 15 min	*o*-Fluoroanisole *p*-Fluoroanisole 2,4-Difluoroanisole	31 21 5
3	2-Naphthol	**1d**	$HCOOH/CH_3OH$ (1/1)	r.t., 15 min	1-Fluoro-2-naphthol[c] 1,1-Difluoro-2-naphthalenone[c]	38 29
4	2-Acetylcyclohexanone	**1d**	HCOOH	20 °C, 30 min	2-Acetyl-2-fluorocyclohexanone[d]	80
5		**1d**	DMF/THF (2/1)	$-60\ ^\circ C \xrightarrow{2.5\ h}$ r.t., 15 min	2-Acetyl-2-fluorocyclohexanone[d]	54
6		**1d**	DMF/THF (1/1)	$-78\ ^\circ C$, 1 h $\xrightarrow{ca. 0.5\ h}$ r.t., 30 min	 [e]	75
7	$Na^+MeC^-(CO_2Et)_2$	**1d**	DMF	$-60\ ^\circ C$, 10 min $\xrightarrow{ca. 10\ min}$ r.t., 1 h	$MeCF(CO_2Et)_2$[e]	64
8	$Na^+PhC^-(CO_2Et)_2$	**1d**	DMF/THF (1/1)	$-78\ ^\circ C \xrightarrow{2.5\ h}$ r.t., 15 min	$PhCF(CO_2Et)_2$[e]	74
9	Styrene	**1d**	CH_3CN/CH_3OH (1/1)	r.t., 3 h	$PhCH(OMe)CH_2F$[e]	25
10	*trans*-$PhCH{=}CHCH_3$	**1d**	CH_3CN/CH_3OH (1/1)	r.t., 10 min	$PhCH(OMe)CHFCH_3$[f]	46
11	*trans*-$PhCH{=}CHCH_3$	**1a**	AcOH	r.t., 15 min	$PhCH(OAc)CHFCH_3$[e,g]	52[h]
12	$PhC(CH_3){=}CH_2$	**1d**	CH_3CN/CH_3OH (1/1)	r.t., 15 min	$PhC(CH_3)(OMe)CH_2F$[i]	70
13		**1d**	CH_3CN	$-20\ ^\circ C$, 20 min	 [k]	81[j]

a) In all runs, each reaction mixture was stirred under argon except for Run 2 (under dry atmosphere). For Runs 1—8 the reaction was carried out in 2 ml of a solvent using 1 mmol of a nucleophile and 1 mmol of **1** except for 3 ml of a solvent in Run 5, for Runs 9—12 the reaction was carried out in 2 ml of a solvent using 2 mmol of a nucleophile and 1 mmol of **1**, and for Run 13 the reaction was carried out in 1 ml of CH_3CN using 0.5 mmol of a nucleophile and 0.5 mmol of **1b**. b) Determined by ^{19}F NMR using fluorobenzene as an internal standard based on a nucleophile used. c) S. Staver and M. Zupan, *J. Org. Chem.*, **50**, 3609 (1985). d) O. Lerman and S. Rozen, *J. Org. Chem.*, **48**, 724 (1983). e) T. Umemoto, S. Fukami, G. Tomizawa, K. Harasawa, K. Kawada, and K. Tomita, *J. Am. Chem. Soc.*, **112**, 8563 (1990). f) The ratio of diastereoisomers was 1/1.4. g) The ratio of diastereoisomers was 1/1.15. h) The formation (47% yield) of another product was observed at −170.6 ppm (in $CDCl_3$) in its ^{19}F NMR spectra, but its structural assignment was not made. i) G. S. Lal, *J. Org. Chem.*, **58**, 2791 (1993). j) A total yield of a 1 : 1.5 mixture of 6*α*- and 6*β*-fluoro steroids. k) R. H. Hesse, *Isr. J. Chem.*, **17**, 60 (1978).

Thus, **1d** readily fluorinated phenol at room temperature to give a 2.4 : 1 mixture of *o*- and *p*-fluorophenols in 41% yield (Run 1). For the fluorination of reactive 2-naphthol, a 1 : 1 mixture of formic acid and methanol was better as a solvent. The fluorination occurred only at the 1-position to give 1-fluoro-2-naphthol and 1,1-difluoro-2-naphthalenone (Run 3). One equimolar amount of less reactive benzene and toluene was treated with **1d** in formic acid under the same conditions (r.t., 15 min), but no fluorinated products were obtained.

Although **1d** is insoluble in acetonitrile, bis(SbF_6) salt **1e** is soluble. And although the fluorination of anisole with **1d** in acetonitrile took 3 d at room temperature to give total 54% yield of fluorinated anisoles, that with **1e** was completed in 15 min to give a total 57% yield (Run 2). Compared with the fluorination of anisole in formic acid (*o*/*p*=1/1, Table 4), fluorination in acetonitrile occurred *o*-selectively to some degree (*o*/*p*=3/2, Run 2).

2-Acetylcyclohexanone, an active methylene compound, was readily fluorinated with **1d** in formic acid at room temperature to give the fluoro product in 80% yield (Run 4). Carbanions of active methylene compounds were fluorinated in DMF or DMF/THF (1/1) at low temperature to give the fluoro products in good yields (Runs 5—8). Styrene reacted with **1d** in a 1 : 1 mixture of acetonitrile and methanol at room temperature for 3 h to give 2-fluoro-1-methoxy-1-phenylethane in 25% yield (Run 9). This was additional evidence indicating the higher reactivity of **1** compared to **5**, since **5** did not react with styrene under similar conditions.[9b)] *trans*-

β-Methylstyrene and *α*-methylstyrene readily reacted with **1d** to give the corresponding fluoro methoxy adducts in 46 and 70% yields, respectively (Runs 10 and 12). The treatment of *trans*-*β*-methylstyrene with bis(triflate) **1a** in acetic acid produced the fluoro acetoxy acdduct in 52% yield (Run 11). The reaction of styrene with **1a** in acetic acid took 5 h at room temperature to give 1-acetoxy-2-fluoro-1-phenylethane in 30% yield, while the reaction with *N*-fluoro-2,3,4,5,6-pentachloropyridinium salts (**6**) was fast (<1 h at room temperature) and the same product was obtained in 72% yield.[5d] This indicates that **1** is less reactive than **6**.

A vinyl acetate of steroid was readily fluorinated with **1d** in acetonitrile at low temperature to give 6-fluoro steroid in 81% yield (Run 13). The ratio of α/β conformation at the 6-position was 1/1.5. The reaction with the corresponding enol trimethylsilyl ether of steroid was vigorous and gave a complex mixture.

Fluorination Mechanism. Two equimolar amounts of anisole were allowed to react with **1a** in acetonitrile under the reflux temperature. This reaction was traced by GC. Thus, the formation of fluoroanisoles increased with the reaction time, and reached the maximum; then, the remaining anisole, the amount of which was nearly one equimolar amount at this time, gradually disappeared to give unidentified products. All of the anisole was consumed in 3 h, and *o*- and *p*-fluoroanisoles were produced in total 62% yield, which was the same as that (45—62%) when one equimolar amount of anisole was used. This clearly indicated that only one N–F in **1** was effective for the fluorination. An ^{19}F NMR tracing experiment supported this; in the reaction of anisole with one equimolar **1a** in acetonitrile-d_3 at ambient temperature, both ^{19}F signals corresponding to the fluorinated anisoles (−121—−136 ppm) and a signal corresponding to HF or F$^-$ (−182.4 ppm) were simultaneously observed along with a decrease in the peak at 39.2 ppm, corresponding to the two N–F's of **1a**. After 24 h, the fluorinated anisoles and HF or F$^-$ were observed to be formed in 57 and 66% yields, respectively. No new signals corresponding to N–F were observed during the reaction. Thus, no mono N–F intermediates, such as **7**, were detected, which might result from salts **1** through fluorination. Similarly, no new signals were observed in the ^{19}F NMR tracing experiment of the reaction between **1a** and 2-acetylcyclohexanone (mol ratio 1 : 1) in acetonitrile-d_3. At ambient temperature, HF or F$^-$(−181.2 ppm) and 2-acetyl-2-fluorocyclohexanone (−156.1 ppm) were formed simultaneously and, in 10 min, their yields were 77 and 83%, respectively.

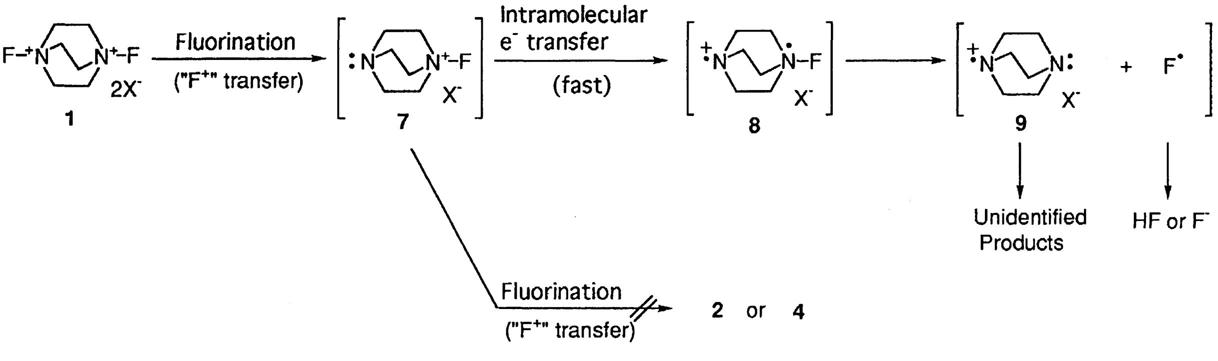
It was reported that **5** fluorinated nucleophiles to reproduce *N*-chloromethyl-4-aza-1-azoniabicylco[2.2.2]octane tetrafluoroborate or its proton salt together with the fluorinated nucleophiles.[9i] However, *N,N′*-difluoro salts **1** did not reproduce **2** or its proton salt **4**, but gave unidentified compounds.

From these results, the whole mechanism between *N,N′*-difluoro salt **1** and a nucleophile was proposed, as shown in Scheme 1. The fluorination of a nucleophile by one N–F of **1** may provide the mono N–F intermediate **7**, which may be immediately converted to diradical cation **8** by an intramolecular one-electron transfer from the free nitrogen atom to the other N–F. It is reasonable that an immediate electron transfer may occur in a molecule in which an easily reducible tertiary amine moiety and a strongly oxidizable N–F moiety exist. The N–F bond of diradical cation **8** may thus be readily broken to result in HF or F$^-$ and the unidentified products. The consumption of 2 equimolar amounts of anisole (as mentioned above) can be explained by the assumption that diradical cation **8**, radical cation **9**, and/or their varient would oxidize the excess of anisole.

The mechanism of the first fluorination step may be similar to that of other known N–F compounds, such as **5**. As the fluorination mechanism, a one-electron transfer mechanism and S$_N$2 mechanism have been proposed.[5d,7e,14)] The dependence of the fluorinating power on the electon density of the nitrogen atoms or the bicyclo[2.2.2]octane nucleus of salts **1** (as discussed above) may suggest that the one-electron transfer mechanism is more likely.

Conclusion

We have synthesized a series of *N,N′*-difluoro-1,4-diazoniabicyclo[2.2.2]octane salts **1a—f** by new methods, and especially demonstrated the usefulness of bis(BF$_4$) salt **1d** as being a highly reactive and easy-to-handle electrophilic fluorinating agent. The present studies have also revealed that the one N–F is effective for fluorination, and that the other N–F plays a role to activate the fluorinating power through the bonds, and has provided significant information



Scheme 1.

concerning the fluorination and its mechanism. From a synthetic point of view, salt **1d** may serve for the commercial production of useful fluoro organic compounds, because it can be economically easily prepared by a one-pot reaction from diamine **2**, which has been produced commercially on a large scale.

Experimental

General. ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded at 200 or 500 MHz, 126 MHz and 188 or 470 MHz, respectively. The solvents for ^{13}C NMR, and ^{19}F NMR were the same as those for ^{1}H NMR, unless otherwise noted. The ^{19}F chemical shifts were given in ppm downfield from $CFCl_3$ as an internal standard. The previously reported fluorination apparatus was used.[5e,5f] A poly(tetrafluoroethylene) flask was used for experiments in which 60% aq HPF_6 or $HSbF_6{\cdot}6H_2O$ were used. The decomposing points were measured using a differential scanning calorimeter; the reported points were the temperatures at which the decomposition began.

Materials. A vinyl acetate of steroid for Run 13 in Table 5 was prepared according to the literature.[15] Proton salts **4a**, **4d**, **4e**, and **4f** (as 2:1 salts of an acid/**2** ratio in Table 1) were prepared by mixing 1,4-diazabicyclo[2.2.2]octane (**2**) with an excess of triflic acid (trifluoromethanesulfonic acid), 85% HBF_4/Et_2O, 60% aq HPF_6, and $HSbF_6{\cdot}6H_2O$, respectively, in dichloromethane or acetonitrile. **4a** and **4d**, which appeared as precipitates from the dichloromethane solution, were isolated by filtrating the reaction mixture and washing with dichloromethane. **4e** and **4f** were isolated by evaporation of the acetonitrile solvent followed by washing the resulting crystals with Et_2O. Diamine **2** of 98% purity available from Aldrich, Inc., was used for the synthesis of **1**. *N*-Chloromethyl-*N'*-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (**5**) was available from Air Products and Chemicals, Inc. Commercially available compounds were used without further purification, unless otherwise noted. The solvents used for the reactions were dried by the usual methods before use.

Synthesis of *N,N'*-Difluoro-1,4-diazoniabicyclo[2.2.2]octane Salts 1a—f. General Procedure: In each experiment, the amounts of 1,4-diazabicyclo[2.2.2]octane (**2**), an acid, and a solvent shown in Table 1 were placed in a flask of the fluorination apparatus. The charged flask was purged with N_2 and placed on a cooling bath at the temperature shown in Table 1. A 10% F_2–90% N_2 (v/v) mixture gas was then introduced at a flow rate 5—10 ml min^{-1} per 1 mmol of **2**, just above the surface of the rapidly stirred reaction mixture. The amounts of F_2 used are given in Table 1. After the flow of F_2 was sopped, only N_2 was passed through the flask at a rate of 20 ml min^{-1} for 10 min. For Runs 3, 8, 9, 11, and 12, proton salts **4a**, **4d**, **4e**, and **4f**, which were prepared and isolated as crystals in separate experiments (as described above), were used as the starting materials, respectively. The post-treatment for Runs 1—4, and 7—11 was as follows: Each reaction mixture was evaporated to dryness under reduced pressure and the residue was washed with some Et_2O to give pure **1a** or **1e**, or a mixture of **1a**, **1d**, or **1e** with the corresponding proton salt **4a**, **4d**, or **4e**. For Run 5, a large amount of Et_2O was added to the reaction mixture, and the resulting precipitate was collected by filtration in a dry box to obtain pure crystals of **1b**. For Run 6, the reaction mixture was concentrated until 4—5 ml of the solvent remained, and a large amount of CH_2Cl_2 was added to give a precipitate, which was collected by filtration in a dry box to obtain pure crystals of **1c**. For Run 12, the reaction mixture was filtered and the filtrate was evaporated to dryness under reduced pressure to give pure crystals of **1f**. The yields of the products are listed in Table 1. In the case where a mixture of **1a**, **1d**, or **1e** with proton salt **4a**, **4d**, or **4e** was obtained, each of the yields was determined by an NMR analysis of the mixture. Although pure crystals of **1a** could also be obtained by recrystallizing the mixture with **4a** from acetonitrile, any attempts to isolate pure **1d** from the mixture with **4d** failed.

Caution. Since F_2 is a highly oxidizing and toxic gas, any experimenter should familiarize him- or herself with the precautions necessary for the safe handling of F_2.[5e,5f] It should be avoided to wash **1c** with Et_2O, because we experienced an explosive decomposition when washing crystals of **1c** with some Et_2O in the filtration procedure in order to isolate **1c** from the reaction mixture.

***N,N'*-Difluoro-1,4-diazoniabicyclo[2.2.2]octane Bis(triflate) (1a):** Decomp temp ca. 170 °C; IR (Nujol) 3039, 1262, 1169, 1037, 867 cm^{-1}; ^{1}H NMR (CD_3CN) δ=5.07 (dd, J=3.5, 3.5 Hz); ^{13}C NMR δ=61.10 (dd, J=11.7, 11.7 Hz); ^{19}F NMR δ=39.2 (2F, br s, 2×NF), −78.1 (6F, s, 2×CF_3). Found: C, 21.42; H, 2.77; N, 6.04%. Calcd for $C_8H_{12}F_8N_2O_6S_2$: C, 21.43; H, 2.70; N, 6.25%.

***N,N'*-Difluoro-1,4-diazoniabicyclo[2.2.2]octane Bis(hydrogensulfate) (1b):** Decomp temp 80 °C; IR (Nujol) 3048, 1266, 1168, 1019, 854 cm^{-1}; ^{1}H NMR (D_2SO_4) δ=4.64 (br s); ^{19}F NMR δ=42.6 (br s, NF). Found: C, 20.75; H, 4.50; N, 7.94%. Calcd for $C_6H_{14}F_2N_2O_8S_2$: C, 20.93; H, 4.10; N, 8.14%.

***N,N'*-Difluoro-1,4-diazoniabicyclo[2.2.2]octane hydrogensulfate Bis(hydrogen fluoride)fluoride (1c):** Decomp temp 100 °C; IR (Nujol) 3051, 1270, 1228, 1045, 874 cm^{-1}; ^{1}H NMR (D_2SO_4) δ=4.64 (br s); ^{19}F NMR (DCOOD) δ=39.8 (br s, NF), −127 (v br peak, HF or F^-). Found: C, 21.49; H, 4.64; N, 8.12; F, 27.9; S, 8.5%. Calcd for $C_6H_{15}F_5N_2O_4S$: C, 21.30; H, 4.47; N, 8.28; F, 28.1; S, 9.5%.

***N,N'*-Difluoro-1,4-diazoniabicyclo[2.2.2]octane Bis(hexafluoroantimonate) (1e):** Decomp temp ca. 200 °C; IR (Nujol) 3067, 1102, 853, 662, 635 cm^{-1}; ^{1}H NMR (CD_3CN) δ=4.96 (dd, J=3.5, 3.5 Hz); ^{19}F NMR δ=38.9 (2F, br s, 2×NF), −96.5—−150.0 (12 F, br m, 2×SbF_6). Found: C, 11.76; H, 1.86; N, 4.43%. Calcd for $C_6H_{12}F_{14}N_2Sb_2$: C, 11.59; H, 1.95; N, 4.51%.

***N,N'*-Difluoro-1,4-diazoniabicyclo[2.2.2]octane Bis(hexafluorophosphate) (1f):** Decomp temp ca. 155 °C; IR (Nujol) 3073, 1103, 861, 831, 559 cm^{-1}; ^{1}H NMR (CD_3CN) δ=4.95 (dd, J=3.5, 3.5 Hz); ^{19}F NMR δ=38.9 (2F, br s, 2×NF), −69.5 (12F, d, J=352 Hz, 2×PF_6). Found: C, 16.58; H, 2.76; N, 6.41%. Calcd for $C_6H_{12}F_{14}N_2P_2$: C, 16.38; H, 2.75; N, 6.37%.

Counteranion Replacement Reaction. General Procedure: Under an argon atmosphere, an acid was added to a stirred solution of a *N,N'*-difluoro-1,4-diazoniabicyclo[2.2.2]octane salt in a solvent; the reaction mixture was then stirred. The acids, solvents, the starting salts, and reaction conditions are shown in Table 2. The resulting precipitate was collected by filtration and washed with some Et_2O to give pure crystals of the *N,N'*-difluoro-1,4-diazoniabicyclo[2.2.2]octane salt. The yields are given in Table 2. The decomposing point and spectral data of pure salt **1d** obtained by this reaction are shown as follows.

***N,N'*-Difluoro-1,4-diazoniabicyclo[2.2.2]octane Bis(tetrafluoroborate) (1d):** Decomp temp ca. 170 °C; IR (Nujol) 3072, 1062, 851 cm^{-1}; ^{1}H NMR (CD_3CN) δ=5.02 (dd, J=3.5, 3.5 Hz); ^{19}F NMR δ=39.2 (2F, br s, 2×NF), −150.2 (8F, s, 2×BF_4). Found: C, 22.35; H, 3.61; N, 8.39%. Calcd for $C_6H_{12}B_2F_{10}N_2$: C, 22.26; H, 3.74; N, 8.65%.

Fluorination and Successive Counteranion Replacement Reaction. General Procedure: A reaction flask charged with 1, 4-diazabicyclo[2.2.2]octane (**2**), sulfuric acid, and 1,1,1,3,3,3-hexafluoro-2-propanol or acetonitrile (the amounts of which are given in Table 3) was purged with N_2 and placed on a cooling bath at the temperature given in Table 3. A 10% F_2–90% N_2 mixture gas was then introduced at a flow rate 5—10 ml $\min^{-1}$ per 1 mmol of **2**, just above the surface of the rapidly stirred reaction mixture in the flask. The amount of F_2 used is given in Table 3. After the flow of F_2 was stopped, only N_2 was passed through the flask at a rate of 20 ml $\min^{-1}$ for 10 min, while the same temperature was maintained. Then, at −20 °C, or room temperature, a Brønsted or Lewis acid was added to the reaction mixture and the mixture was stirred at −20 °C to room temperature for 10 min or at room temperature for 15 min. The reaction temperature and the Brønsted or Lewis acid for each reaction are given in Table 3. The post-treatment was carried out in a similar manner as described for the counteranion replacement reaction above, to obtain pure or almost-pure crystals of **1d**, **1e**, or **1f**. The yields are given in Table 3.

Fluorination of Anisole with *N,N′*-Difluoro-1,4-diazoniabicyclo[2.2.2]octane Salts 1a, 1b, 1d, and 1e and *N*-Chloromethyl-*N′*-fluoro-1,4-diazoniabicyclo[2.2.2]octane Bis(tetrafluoroborate) (5). Into a stirred solution of 1 mmol of anisole in 2 ml of formic acid at room temperature was added 1 mmol of **1a**, **1b**, **1d**, **1e**, or **5**; the reaction mixture was then stirred for 15 min at room temperature under argon or a dry atmosphere. The treatment and reaction of **1b** was carried out in a dry box filled with argon, because of the hygroscopic nature of **1b**. The reaction was quenched with 5 ml of 0.5 M (M=mol dm^{-3}) aq $Na_2S_2O_3$ solution, and the reaction mixture was extracted with Et_2O. The yields were determined by GC and ^{19}F NMR analyses of the extract (tridecane and fluorobenzene as internal standards). The yields were calculated on the basis of the used anisole. The results are given in Table 4.

Electrophilic Fluorination of Various Nucleophiles with *N,N′*-Difluoro-1,4-diazoniabicyclo[2.2.2]octane Salts 1a, 1d, or 1e. General Procedure: For Runs 1—8 in Table 5, 1 mmol of **1d** or **1e** was added to a stirred solution of 1 mmol of a nucleophile in 2 ml of a solvent; the reaction mixture was then stirred under argon or a dry atmosphere. For Runs 9—12, 1 mmol of **1a** or **1d** was added to a stirred solution of 2 mmol of a nucleophile in 2 ml of a solvent; the reaction mixture was then stirred under argon. For Run 13, 0.5 mmol of **1d** was added to a stirred solution of 0.5 mmol of a nucleophile in 1 ml of CH_3CN; the reaction mixture was then stirred under argon. The nucleophiles, the solvents, and the reaction conditions are given in Table 5. The *N,N′*-difluoro-1,4-diazoniabicyclo[2.2.2]octane salts used were consumed at the reaction times shown in Table 5. For Runs 1—4, after 5 ml of 0.5 M aq $Na_2S_2O_3$ solution was added to the reaction mixture, the mixture was extracted with Et_2O. The extract was washed with saturated NaCl aq solution and dried with anhydrous $MgSO_4$. The thus-obtained ethereal extract was analyzed by ^{19}F NMR (fluorobenzene as an internal standard) and/or GC (tridecane or heptadecane as an internal standard) to determine the yields of fluoro products. For Runs 5—13, the yields were determined by ^{19}F NMR of reaction mixture (fluorobenzene as an internal standard). The fluoro products and their yields are summarized in Table 5.

A structural assignment of the products was carried out by a spectral analysis or comparison with those of authentic samples. The spectral data agreed with the assigned structures or the data of authentic samples. A new compound was isolated by column chromatography of the residue, which was obtained from the ethereal extract, on silica gel using hexane as an eluent; its spectral data are given below.

2-Fluoro-1-methoxy-1-phenylpropane: Oil; for a major isomer ^1H NMR ($CDCl_3$) $\delta=1.31$ (3H, dd, $J=6.30$, 24.25 Hz, CH_3), 3.32 (3H, s, OCH_3), 4.25 (1H, dd, $J=4.45$, 14.05 Hz, PhCH), 4.75 (1H, ddq, $J=4.45$, 48.40, 6.30 Hz, CHF), 7.3—7.4 (5H, m, aromatic protons); ^{19}F NMR $\delta=-180.2$ (ddq, $J=14.05$, 24.25, 48.40 Hz); for a minor isomer ^1H NMR ($CDCl_3$) $\delta=1.12$ (3H, dd, $J=6.35$, 24.05 Hz, CH_3), 3.28 (3H, s, OCH_3), 4.18 (1H, dd, $J=6.65$ 13.40 Hz, PhCH), 4.72 (1H, ddq, $J=6.65$, 47.30, 6.35 Hz, CHF), 7.3—7.4 (5H, m, aromatic protons); ^{19}F NMR $\delta=-179.9$ (ddq, $J=13.40$, 24.05, 47.30 Hz); IR (neat)(as a 1.4 : 1 mixture of diastereoisomers) 2935 (OCH_3) cm^{-1}; MS *m/z* 168 (M^+). Millimass Found; *m/z* 168.09601. Calcd for $C_{10}H_{13}FO$: M, 168.09504.

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