Power and Structure-Variable Fluorinating Agents. The *N*-Fluoropyridinium Salt System

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Abstract: The usefulness of the *N*-fluoropyridinium salt system as a source of fluorinating agents was examined by using substituted or unsubstituted *N*-fluoropyridinium triflates **1–11**, *N*-fluoropyridinium salts possessing other counteranions **1a–d** and **3a**, and the counteranion-bound salts, *N*-fluoropyridinium-2-sulfonates **12** and **13**. Electrophilic fluorinating power was found to vary remarkably according to the electronic nature of the ring substituents. This power increased as the electron density of positive nitrogen sites decreased, and this was correlated to the pK_a values of the corresponding pyridines. By virtue of this variation, it was possible to fluorinate a wide range of nucleophilic substrates differing in reactivity. It is thus possible to fluorinate aromatics, carbanions, active methylene compounds, enol alkyl or silyl ethers, vinyl acetates, ketene silyl acetals, and olefins through the proper use of salts pentachloro **6** through 2,4,6-trimethyl **2**, their power decreasing in this order. All the reactions could be explained on the basis of a one-electron-transfer mechanism. *N*-Fluoropyridinium salts showed high chemoselectivity in fluorination, the extent depending on the reactive moiety. In consideration of these findings, selective 9α-fluorination of steroids was carried out by reacting **1** with tris(trimethylsilyl ether) **73** of a triketo steroid. Regio- or stereoselectivity in fluorination was determined by a *N*-fluoropyridinium salt structure. Steric bulkiness of the N–F surroundings hindered the ortho fluorination of phenols and aniline derivatives, while the capacity for hydrogen bonding on the part of the counteranions prompted this process, and the counteranion-bound salts **12** and **13** underwent this fluorination exclusively or almost so. Both bulky *N*-fluoropyridinium triflates **2** and **7** preferentially attacked the 6-position of the conjugated vinyl ester of a steroid from the unhindered β-direction to give a thermally unstable 6β-fluoro isomer. On the basis of these results, *N*-fluoropyridinium salts may be concluded to constitute a system that can serve as a source of the most ideal fluorinating agents for conducting desired selective fluorination through fluorinating capacity or structural alteration.

Introduction

Since fluorinated organics are particularly significant from the standpoint of biological activity provided a specific site of an organic molecule is substituted with a fluorine atom(s),[2] much effort has been made to develop new reagents and methods for selective fluorination.[3] Electrophilic fluorinating agents such as F_2,[4] CF_3OF,[5] $FClO_3$,[6] $PhIF_2$,[7] CF_3COOF,[8] CH_3COOF,[9] XeF_2,[10] and $CsSO_4F$[11] require special equipment and techniques due to their explosive, toxic, unstable, and hygroscopic qualities. *N*-Fluoroperfluoropiperidine,[12] *N*-fluoropyridone,[13] and *N*-fluoro-*N*-alkylarenesulfonamides[14] are easy to handle but have low reactivity. Reactive agents are thus difficult to handle, while those that are stable have a limited scope of application. *N*-Fluoroquinuclidinium salts,[15] *N*-fluoroperfluoroalkylsulfonamides,[16] and *N*-fluorosultums[17] are the most recently developed reagents.

Various stable *N*-fluoropyridinium salts were synthesized as described in a previous paper.[18] In our preliminary studies,[19] certain *N*-fluoropyridinium triflates were found to function as useful fluorinating agents differing in power. Extensive studies on the fluorinating reactivities of various *N*-fluoropyridinium salts indicate the electrophilic fluorinating power of *N*-fluoropyridinium salts to change greatly with reduction in the electron density of the N^+–F site and variation in power according to ring substituents to make possible the fluorination of a wide variety of substrates differing in reactivity, while structural variation arising from ring substituents or counteranion parts greatly reflects selectivity in fluorination. This paper describes new fluorinating agents that comprise the *N*-fluoropyridinium salt system, their power, structural variation, and applications to mild and selective fluorinations.

Experimental Section

General Methods. The structure assignment of the reaction products was carried out by comparison of authentic samples or by spectral

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analyses. Data of new compounds are shown in each section. Melting points were uncorrected. Distillation was done by using a glass tube oven, and the boiling points were bath temperatures. ^1H NMR spectra were recorded with a Varian XL-100 or EM 390 NMR spectrometer or a Bruker AM-400 NMR spectrometer with tetramethylsilane as an internal standard. ^{19}F NMR spectra were measured with a Varian XL-100 or XL-300 NMR spectrometer or a Hitachi R-20B NMR spectrometer. ^{19}F NMR chemical shifts were reported in ppm upfield from trichlorofluoromethane as an internal standard. Chloroform-*d* was used as a solvent for ^1H and ^{19}F NMR, unless otherwise noted. IR spectra were measured on a Jasco A-202 diffraction grating infrared spectrometer. GC analyses were carried out on a Shimazu gas chromatograph with a column (3–4 m × 3 mm) packed with PEG-20M on Support B for fluorinated anisoles, one packed with KG-02 on Uniport for fluorinated phenols, or one packed with SE-30 on Chromosorb W AW DMCS for other products.

Materials. *N*-Fluoropyridinium salts were prepared according to methods reported in our previous paper.[18] An enol ethyl ether, vinyl acetates, enol trimethylsilyl ethers, and enamines of steroids and other enol ethers were prepared according to well-known methods.[20] 5β-Androstan-3,11,17-trione was prepared in 66% yield along with its 5α-isomer (22%) from commercially available androst-4-en-3,11,17-trione by hydrogenation on Pd/C in ethanol containing 10% hydrochloric acid.[21] The solvents used for the reactions were dried by usual methods before use. Other commercially available compounds were used without further purification, unless otherwise noted.

Controlled Fluorination of Anisole with *N*-Fluoropyridinium Triflates 1–6. A *N*-fluoropyridinium triflate (0.5 mmol) was added to a solution of 0.5 mmol of anisole in 2 mL of a halocarbon, and the mixture was stirred under argon atmosphere at the temperature shown in Table I. Each reaction temperature was set so as to allow the *N*-fluoropyridinium triflate to react with anisole smoothly. The ending point of the reaction was the time when the triflate was consumed. It was checked by using an aqueous potassium iodide solution. After the reaction was finished, the reaction mixture was analyzed by GLC. The results are shown in Table I.

Fluorination of Aromatics. General Procedure. A *N*-fluoropyridinium triflate (1 mmol) was added to a solution of 1 mmol of a substrate in 2–3 mL of a solvent. The solvents and the reaction conditions are shown in Tables II–V and in the Results section. ^{19}F-NMR yields or GLC yields were determined by analyzing the reaction mixtures of which reactions finished. For isolation of fluoro products, after some diethyl ether was added to the reaction mixture, the organic layer was washed with water, dried with anhydrous magnesium sulfate, filtered, and evaporated. The resulting residue was purified by the usual methods such as column chromatography on silica gel, distillation, recrystallization, or GLC according to the fluoro products. **22** and **23** could not be separated from each other. **Methyl 3-fluoro-4-hydroxybenzoate**: mp 91–93 °C; ^1H NMR δ 3.88 (3 H, s, CH_3), 5.5–6.3 (1 H, OH), 7.00 (1 H, dd, J = 8, 8 Hz, 5-H), 7.75 (2 H, d, J = 10 Hz, 2, 6-H); ^{19}F NMR 138.4 (br s); IR (KBr) 3200 (OH), 1695 (CO) cm^{-1}; mass spectrum, m/e 170 (M^+). **Methyl 3-(3′-fluoro-4′-hydroxyphenyl)-2-phthalimidopropanate (20)**: mp 108–109 °C; ^1H NMR δ 3.46 (2 H, m, CH_2), 3.76 (3 H, s, CH_3), 5.07 (1 H, dd, J = 7.8, 10.8 Hz, CH), 5.79 (1 H, br s, OH), 6.7–7.0 (3 H, m), 7.6–7.9 (4 H, m): ^{19}F NMR 137.3 (s); IR (KBr) 3250 (OH), 1755 (COO), 1700 (CON) cm^{-1}. **2- and 4-Fluoroestrone (22) and (23)**: ^1H NMR (400 MHz) δ 0.91 (3 H, s, CH_3), 6.72 (1 H, d, J = 9.1 Hz, 4-H for **22**), 6.81 (1 H, dd, J = 9.0, 9.0 Hz, 2-H for **23**), 6.94 (1 H, d, J = 9.0 Hz, 1-H for **23**), 6.97 (1 H, d, J = 12.8 Hz, 1-H for **22**); ^{19}F NMR 144.5 (dd, J = 13, 9 Hz for **22**), 145.8 (d, J = 9 Hz, for **23**); IR (KBr) 3270 (OH), 1722 (CO) cm^{-1}; mass spectrum, m/e 288(M^+). **Methyl 3-fluoro-4-hydroxyphenylacetate (28)**: oil; ^1H NMR δ 3.50 (2 H, s, CH_2), 3.63 (3 H, s, CH_3), 5.37 (1 H, br s, OH), 6.70–7.10 (3 H, m, phenyl); ^{19}F NMR 140.3 (s); IR (KBr) 3400 (OH), 1720 (CO) cm^{-1}; mass spectrum, m/e 184 (M^+). **4-Fluoro-4-[(methoxycarbonyl)-methyl]cyclohexa-2,5-dien-1-one (29)**: oil; ^1H NMR δ 2.90 (2 H, d, J = 17.2 Hz, CH_2), 3.64 (3 H, s, CH_3), 6.1–6.2 (2 H, m), 6.7–7.1 (2 H, m); ^{19}F NMR 149.6 (t, J = 17.2 Hz); IR (KBr) 1740 (COO), 1680 (CO), 1640 (C=C) cm^{-1}; mass spectrum, m/e 198 (M^+). Anal. Calcd for $C_9H_9FO_3$: C, 58.69; H, 4.93. Found: C, 58.87; H, 5.06. **Methyl 3-fluoro-4-methoxyphenylacetate (25)**: oil; ^1H NMR δ 3.49 (2 H, s, CH_2), 3.68 (3 H, s, CH_3), 3.84 (3 H, s, CH_3), 6.8–7.2 (3 H, m); ^{19}F NMR 134.6 (s); IR (neat) 1740 (CO) cm^{-1}; mass spectrum, m/e 198 (M^+). ***N*-Benzyl-2-(ethoxycarbonyl)-3-fluoroindole**: mp 69.5–70.5 °C (hexane); ^1H NMR δ 1.33 (3 H, t, J = 7 Hz, CH_3), 4.31 (2 H, q, J = 7 Hz, CH_2), 5.70 (2 H, s, NCH_2), 6.90–7.75 (9 H, m, phenyl); ^{19}F NMR 154.1 (s); IR (nujol) 1700 (CO) cm^{-1}; millimass spectrum 297.1173 (calcd for $C_{18}H_{16}FNO$ 297.1166). **(2-Fluoro-4-methylphenyl)urethane**: mp 49–50 °C; ^1H NMR δ 1.31 (3 H, t, J = 7.1 Hz, CH_3), 2.28 (3 H, s, CH_3), 4.27 (2 H, q, J = 7.1 Hz, CH_2), 6.70–6.78 (1 H, br s, NH), 6.83–6.93 (2 H, m), 7.90 (1 H, t, J = 8.4 Hz); ^{19}F NMR 133.1 (s); IR (KBr) 3450, 3320, 1700 (CO) cm^{-1}; mass spectrum, m/e 197 (M^+).

Table I. Controlled Fluorination of Anisole with *N*-Fluoropyridinium Triflates

salt (1 equiv)	solv	temp (°C)	time (h)	conv[a] (%)	product (yield[b] (%)) 14	15
2	$(CHCl_2)_2$	147	10	68	42	*c*
1	$(CHCl_2)_2$	120	18	72	36	*c*
3	$(CH_2Cl)_2$	83	18	65	48	50
4	CH_2Cl_2	40	23	71	44	48
5	CH_2Cl_2	40	7	71	41	41
6	CH_2Cl_2	rt	0.25	91	36	38

[a] Determined by GLC. [b] Determined by GLC on the basis of the consumed anisole. [c] The yields could not be determined because of overlapped impurities of the solvent used.

Fluorination of Carbanions. Typical Procedure. At room temperature, 1 mmol of *N*-fluoro-2,4,6-trimethylpyridinium triflate (**2**) was added in several portions into a THF solution of sodium salt of diethyl phenylmalonate, which was in situ prepared by treating 1 mmol of diethyl phenylmalonate with 1 mmol of 60% sodium hydride in oil in 2 mL of THF at 0 °C. After 30 min, the reaction mixture was poured into dilute hydrochloric acid and extracted with diethyl ether. The extract was washed with aqueous sodium bicarbonate solution and then with water, dried with anhydrous magnesium sulfate, filtered, and evaporated. The resulting residue was column chromatographed on silica gel by using a 1:1 mixture of methylene chloride and hexane as an eluent to give diethyl fluorophenylmalonate as an oil in 83% yield. **Diethyl phenyl(2-pyridyl)malonate (38)**: mp 103–105 °C; ^1H NMR δ 1.27 (6 H, t, J = 6.7 Hz, CH_3), 4.30 (4 H, q, J = 6.7 Hz, CH_2), 7.00–7.35 (7 H, m, phenyl and 3,5-H), 7.55 (1 H, m, 4-H), 8.52 (1 H, m, 6-H); IR (KBr) 1730 (CO) cm^{-1}; mass spectrum, m/e 313 (M^+). Anal. Calcd for $C_{18}H_{19}NO_4$: C, 69.00; H, 6.07; N, 4.47. Found: C, 69.03; H, 6.17; N, 4.40. **Diethyl phenyl(4-*tert*-butyl-2-pyridyl)malonate (39)**: bp 190 °C/4 mmHg; ^1H NMR δ 1.26 (9 H, s, *t*-Bu), 1.27 (6 H, t, J = 7.1 Hz, CH_3), 4.34 (4 H, q, J = 7.1 Hz, CH_2), 7.19 (1 H, dd, J = 5.3, 1.9 Hz, 5-H), 7.23–7.32 (5 H, m, phenyl), 7.62 (1 H, dd, J = 1.8, 0.7 Hz, 3-H), 8.46 (1 H, dd, J = 5.3, 0.7 Hz, 6-H): IR (neat) 1740 (CO) cm^{-1}; mass spectrum, m/e 369 (M^+). Anal. Calcd for $C_{22}H_{27}NO_4$: C, 71.54; H, 7.32; N, 3.79. Found: C, 71.41; H, 7.39; N, 3.73. **Diethyl phenyl(2,6-dimethyl-4-pyridyl)malonate (40)**: bp 190 °C/4 mmHg; ^1H NMR δ 1.23 (6 H, t, J = 7.5 Hz, CH_3), 2.48 (6 H, s, CH_3), 4.58 (4 H, q, J = 7.5 Hz, OCH_2), 6.95 (2 H, s, pyridyl), 7.28 (5 H, m, phenyl); IR (KBr) 1735 (CO) cm^{-1}; mass spectrum, m/e 341 (M^+). Anal. Calcd for $C_{20}H_{23}NO_4$: C, 70.18; H, 7.02; N, 4.09. Found: C, 70.28; H, 6.75; N, 3.99. **2-Fluoro-2-methyl-1,3-cyclopentadione**: ^1H NMR δ 1.53 (3 H, d, J = 22.5 Hz, CH_3), 2.6–3.2 (4 H, m, CH_2); ^{19}F NMR 172.5 (q, J = 22.5 Hz). **Fluoro(phenyl)malononitrile**: ^1H NMR δ 7.3–7.8 (m, phenyl); ^{19}F NMR 118.9 (s). **Ethyl (phenylsulfonyl)fluoroacetate**: bp 150–160 °C/1 mmHg; ^1H NMR δ 1.30 (3 H, t, J = 7.5 Hz, CH_3), 4.28 (2 H, q, J = 7.5 Hz, CH_2), 5.57 (1 H, d, J = 48.0 Hz, CHF), 7.43–8.10 (5 H, m, phenyl); ^{19}F NMR 180.9 (d, J = 48.0 Hz); IR (neat) 1760, 1450, 1340, 1240 cm^{-1}; mass spectrum, m/e 246 (M^+). Anal. Calcd for $C_{10}H_{11}FO_4S$: C, 48.77; H, 4.50. Found: C, 48.64; H, 4.65. **Ethyl (phenylsulfonyl)difluoroacetate**: oil; ^1H NMR δ 1.38 (3 H, t, J = 6.6 Hz, CH_3), 4.43 (2 H, q, J = 6.6 Hz, CH_2), 7.47–8.17 (5 H, m, phenyl); ^{19}F NMR 107.6 (s); IR (neat) 1770, 1445, 1355, 1300 cm^{-1}; mass spectrum, m/e 264 (M^+). **Diethyl chlorofluoromalonate**: bp 120–130 °C/30 mmHg; ^1H NMR δ 1.35 (6 H, t, J = 7.2 Hz, CH_3), 4.35 (4 H, q, J = 7.2 Hz, CH_2); ^{19}F NMR 120.0 (s); IR (neat) 1780 (CO) cm^{-1}; mass spectrum, m/e 215 ($M^+ + 3$), 213 ($M^+ + 1$). Anal. Calcd for $C_7H_{10}ClFO_4$: C, 39.55; H, 4.74. Found: C, 39.43; H, 4.57.

Lewis Acid-Catalyzed Fluorination of Active Methylene Compounds. General Procedure. In a flask, 50–56 mg (ca. 0.4 mmol) of zinc chloride was placed and dried at 120–130 °C for ca. 1 h under vacuum. After that, the flask was filled with argon and cooled to room temperature. To the flask were added 2 mL of dichloroethane, 1 mmol of an active methylene compound, and 1 or 2 mmol of *N*-fluoro-2,4,6-trimethylpyridinium triflate (**2**). The mixture was stirred under the conditions shown in Table VII. After the reaction, the usual post-treatment was carried out for the isolation of the fluoro products. Aluminum chloride was used without predrying. **2,2-Difluoro-1,3-diphenyl-1,3-propanedione (44)**: mp 60–61 °C (hexane); ^1H NMR δ 7.32–7.77 (6 H, m, phenyl),

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7.95–8.23 (4 H, m, phenyl); ^{19}F NMR 102.8 (s); IR (KBr) 1700 (CO)) cm^{-1}; mass spectrum, *m/e* 260 (M$^+$). Anal. Calcd for $C_{15}H_{10}F_2O_2$: C, 69.23; H, 3.87. Found: C, 69.28; H, 3.97. **2-Fluoro-1,3-diphenyl-1,3-propanedione (45)**: mp 72–75 °C (hexane); ^{1}H NMR δ 6.50 (1 H, d, J = 48.0 Hz, CHF), 7.30–7.73 (6 H, m, phenyl), 7.90–8.20 (4 H, m, phenyl); ^{19}F NMR 186.8 (d, J = 48.0 Hz); IR (KBr) 1670 (CO) cm^{-1}; mass spectrum, *m/e* 242 (M$^+$). Anal. Calcd for $C_{15}H_{11}FO_2$: C, 74.37; H, 4.57. Found: C, 74.46; H, 4.52. **Ethyl 2,2-difluoroacetoacetate**: ^{1}H NMR δ 1.37 (3 H, t, J = 7.2 Hz, CH_3), 2.42 (3 H, t, J = 1.8 Hz, $COCH_3$), 4.38 (2 H, q, J = 7.2 Hz, CH_2); ^{19}F NMR 112.5 (s); IR (neat) 1780, 1760 cm^{-1}; mass spectrum, *m/e* 166 (M$^+$).

Fluorination of Enol Alkyl Ethers. General procedure is the same as for the fluorination of aromatics. The used amount of enol alkyl ethers is 1 equiv to *N*-fluoropyridinium salt **1** except for **46** and **48** of which the amount was 1.2–1.4 equiv. The reaction conditions are shown in eqs 3–6 and Scheme II. In the fluorination of dihydrofuran **48**, 2 mol % of pyridine was added to the reaction mixture. For isolation of salts **47** and **49**, diethyl ether was added to the reaction mixture, and the resulting oil was isolated by a decantation method. The oil was again dissolved in methylene chloride, and diethyl ether was added to the solution. The resulting oil was isolated and dried under vacuum. In the case of 1-methoxycyclohexene, after a mixture of **1** and 1-methoxycyclohexene in methylene chloride was stirred for 2–4 h at room temperature, an amount of water was added to the reaction mixture, and the mixture was stirred for 1 h at room temperature in order to carry out the acid hydrolysis, giving **55** in 60% overall yield. ***N*-(3-Fluoro-2,3,5,6-tetrahydro-2-pyranyl)pyridinium triflate (47)**: ^{1}H NMR (CD_3CN) δ 1.10–2.54 (4 H, m, CH_2CH_2), 3.70–4.50 (2.5 H, m, CH_2O and $^1/_2$ CHF), 5.07 ($^1/_2$ H, dm, J = 51 Hz, CHF for trans or cis isomer), 5.90 ($^1/_2$ H, dd, J = 9.0, 3.8 Hz, CHN for trans or cis isomer) 6.15 ($^1/_2$ H, d, J = 22.5 Hz, CHN for trans or cis isomer), 8.03–9.15 (5 H, m, pydinium); ^{19}F NMR (CD_3CN) 77.3 (3 F, s, CF_3), 185.3 ($^1/_2$ F, d, J = 51 Hz, CF for trans or cis isomer), 205.9 ($^1/_2$ F, ddd, J = 51, 51, 21 Hz, CF for trans or cis isomer); IR (KBr) 1630, 1480, 1260, 1157, 1025 cm^{-1}. ***N*-(3-Fluoro-2,3,4,5-tetrahydro-2-furanyl)pyridinium triflate (49)**: ^{1}H NMR (CD_3CN) δ 2.1–3.0 (2 H, m, CH_2), 4.28–4.85 (2 H, m, CH_2O), 5.57 ($^1/_2$ H, dm, J = 48 Hz for trans or cis isomer), 5.70 ($^1/_2$ H, dm, J = 53 Hz, CHF for trans or cis isomer), 6.41–6.69 (1 H, m, CHN), 8.0–9.05 (5 H, m, pyridinium); ^{19}F NMR (CD_3CN) 77.8 (s, CF_3), 181.7 (m, CF for trans or cis isomer), 192.9 (m, CF for trans and cis isomer); IR (KBr) 1610, 1480, 1260, 1155, 1025 cm^{-1}.

Preparation of 5-Fluorouracil Derivatives 50α, 50β, 51α, and 51β. General Procedure: *N,N'*-Bis(trimethylsilyl)-5-fluorouracil (1.03 mmol) was added to a solution of 1.49 mmol of **47** or **49** in 2 mL of *N,N*-dimethylformamide, and the mixture was stirred on an oil bath of 120 °C for 4 h under argon atmosphere. The reaction mixture was poured into water and extracted with methylene chloride. The extract was dried with anhydrous magnesium sulfate, filtered, and evaporated. The resulting two isomeric 5-fluorouracil derivatives were separated by column chromatography on silica gel by using a 1:1 mixture of ethyl acetate and hexane as an eluent. **5-Fluoro-1-(*trans*-3′-fluoro-2′,3′,5′,6′-tetrahydro-2′-pyranyl)uracil (50α)**: mp 226–231 °C (with dec) (ethyl acetate–hexane); ^{1}H NMR (CD_3CN–DMSO-d_6) δ 1.46–2.56 (m, CH_2CH_2), 3.37–4.10 (2 H, m, 5′-H), 4.53 (1 H, dm, J = 47.0 Hz, 2′-H), 5.50 (1 H, dm, J = 9.0 Hz, 1′-H), 7.61 (1 H, d, J = 7.2 Hz, 6-H); ^{19}F NMR (CD_3CN–DMSO-d_6) 165.7 (d, 5-F), 185.2 (d, J = 47 Hz, 2′-F); IR (KBr) 3450, 1730, 1710, 1660, 1260, 1080 cm^{-1}. Anal. Calcd for $C_9H_{10}F_2N_2O_3$: C, 46.56; H, 4.34; N, 12.06. Found: C, 46.61; H, 4.37; N, 12.10. **5-Fluoro-1-(*cis*-3′-fluoro-2′,3′,5′,6′-tetrahydro-2′-pyranyl)uracil (50β)**: mp 205–207 °C (ethyl acetate–hexane); ^{1}H NMR (CD_3CN–DMSO-d_6) δ 1.30–2.60 (m, CH_2CH_2), 3.57–4.26 (2 H, m, 5′-H), 4.70 (1 H, br d, J = 49.5 Hz, 2′-H), 5.54 (1 H, d, J = 25.2 Hz, 1′-H), 7.62 (1 H, dd, J = 7.2, 1.5 Hz, 6-H); ^{19}F NMR (CD_3CN–DMSO-d_6) 168.0 (d, 5-F), 204.4 (m, 2′-F); IR (KBr) 3450, 1730, 1700, 1670, 1260, 1100 cm^{-1}. Anal. Calcd for $C_9H_{10}F_2N_2O_3$: C, 46.56; H, 4.34; N, 12.06. Found: C, 46.43; H, 4.28; N, 12.03. **5-Fluoro-1-(*trans*-3′-fluoro-2′,3′,4′,5′-tetrahydro-2′-furanyl)uracil (51α)**: mp 209–215 °C (with dec) (ethyl acetate–hexane); ^{1}H NMR (CD_3CN–DMSO-d_6) δ 2.15–2.50 (2 H, m, 3′-H), 4.07 (1 H, dd, J = 16.5, 8.3 Hz, 4′-H), 4.38 (1 H, dd, J = 11.3, 8.3 Hz, 4′-H), 5.21 (1 H, dm, J = 51.3 Hz, 2′-H), 5.77 (1 H, d, J = 13.5 Hz, 1′-H), 7.44 (1 H, d, J = 6.3 Hz, 6-H); ^{19}F NMR (CD_3CN–DMSO-d_6) 166.8 (d, 5-F), 180.0 (m, 2′-F); IR (KBr) 3450, 1710, 1680, 1260, 1110, 1095 cm^{-1}. Anal. Calcd for $C_8H_8F_2N_2O_3$: C, 44.05; H, 3.70; N, 12.84. Found: C, 43.98; H, 3.63; N, 12.72. **5-Fluoro-1-(*cis*-3′-fluoro-2′,3′,4′,5′-tetrahydro-2′-furanyl)uracil (51β)**: mp 161–163 °C (ethyl acetate–hexane); ^{1}H NMR (CD_3CN–DMSO-d_6) δ 2.01–2.68 (2 H, m, 4′-H), 3.90–4.40 (2 H, m, 5′-H), 5.25 (1 H, ddd, J = 54.0, 6.0, 3.0 Hz, 3′-H), 5.93 (1 H, ddd, J = 18.0, 3.0, 1.5 Hz, 2′-H), 7.59 (1 H, dd, J = 6.3, 1.5 Hz, 6-H); ^{19}F NMR (CD_3CN–DMSO-d_6) 167.6 (d, 5-F), 192.0 (m, 3′-F); IR (KBr) 3500, 1710, 1680, 1265, 1120, 1085 cm^{-1}. Anal. Calcd for $C_8H_8F_2N_2O_3$: C, 44.05; H, 3.70; N, 12.84. Found: C, 44.06; H, 3.78; N, 12.71. **3-Fluoro-2-isopropoxy-2,3,5,6-tetrahydropyran (52)** (as a 1.5:1 isomeric mixture): oil; ^{1}H NMR (400 MHz) δ 1.14–1.36 (6 H, m, CH_3), 1.40–2.11 (4 H, m, 4-H, 5-H), 3.42–3.58 (1 H, m, OCH), 3.74–4.03 (2 H, m, 6-H), 4.32 (dddd, J = 48.1, 5.3, 3.1, 3.1 Hz, 3-H for minor product), 4.48 (dddd, J = 48.3, 10.7, 4.6, 3.2 Hz, 3-H for major product), 4.73 (dd, J = 7.0, 3.1 Hz, 2-H for minor product), 4.88 (dd, J = 3.2, 3.2 Hz, 2-H for major product); ^{19}F NMR (282.2 MHz) 189.1 (d, J = 43.5 Hz for major product), 190.1 (ddm, J = 41.9, 41.9 Hz for minor product); mass spectrum, *m/e* 162 (M$^+$). Anal. Calcd for $C_8H_{15}FO_2$: C, 59.24; H, 9.32. Found: C, 59.04; H, 9.40. **6-Fluoro-1-methoxy-1-cyclohexene (54)**: ^{1}H NMR δ 1.30–2.30 (6 H, m), 3.56 (3 H, s, CH_3), 4.82 (1 H, dm, J = 51 Hz, CHF), 4.90 (1 H, m, 2-H); ^{19}F NMR 177.2 (m). **6α-Fluoro-4-androsten-17β-ol-3-one (60α)**: mp 161–164 °C (ethyl acetate–hexane); ^{1}H NMR δ 0.80 (3 H, s, 13-CH_3), 1.20 (3 H, s, 10-CH_3), 3.67 (1 H, t, J = 7.5 Hz, 17-H), 5.12 (1 H, dm, J = 48.0 Hz, 6-H), 6.08 (1 H, m, 4-H); ^{19}F NMR 182.6 (d, J = 48 Hz); IR (KBr) 3450 (OH), 1666 (CO) cm^{-1}; mass spectrum, *m/e* 306 (M$^+$). Anal. Calcd for $C_{19}H_{27}FO_2{\cdot}H_2O$ (monohydrate): C, 70.34; H, 9.01. Found: C, 70.33; H, 8.97. **6β-Fluoro-4-androsten-17β-ol-3-one (60β)**: mp 166–168 °C (with dec) (ethyl acetate–hexane); ^{1}H NMR δ 0.84 (3 H, s, 13-H), 1.30 (3 H, d, J = 1.7 Hz, 10-CH_3), 3.60 (1 H, t, J = 8.0 Hz, 17-H), 4.97 (1 H, dm, J = 49.5 Hz, 6-H), 5.90 (1 H, d, J = 4.8 Hz, 4-H); ^{19}F NMR 165.0 (t, J = 50 Hz); IR (KBr) 3500 (OH), 1680 (CO) cm^{-1}; mass spectrum, *m/e* 306 (M$^+$). Anal. Calcd for $C_{19}H_{27}FO_2$: C, 74.48; H, 8.88. Found: C, 74.41; H, 8.85. **4-Fluoro-5-androsten-17β-ol-3-one (62)**: mp 164–168 °C (ethyl acetate–hexane); ^{1}H NMR δ 0.80 (3 H, s, 13-CH_3), 1.27 (3 H, s, 10-CH_3), 3.65 (1 H, t, J = 7.5 Hz, 17-H), 5.52 (1 H, dm, J = 50.0 Hz, 4-H), 5.80 (1 H, m, 6-H); ^{19}F NMR 205.6 (d, J = 50 Hz); IR (KBr) 3500 (OH), 1735 (CO), 1687 (C=C) cm^{-1}; mass spectrum, *m/e* 306 (M$^+$). Anal. Calcd for $C_{19}H_{27}FO_2{\cdot}^1/_4H_2O$: C, 73.40; H, 8.91. Found: C, 73.47; H, 8.90.

Fluorination of Vinyl Esters. General procedure is the same as for the fluorination of aromatics. The reaction conditions are shown in Tables IX and X and eq 7. **17-Acetoxy-6α-fluoro-4,16-androstadien-3-one (65α)**: mp 146–148 °C (hexane); ^{1}H NMR δ 0.95 (3 H, s, 13-CH_3), 1.22 (3 H, s, 10-CH_3), 2.14 (3 H, s, $COCH_3$), 5.12 (1 H, dm, J = 49.5 Hz, 6-H), 5.53 (1 H, m, 16-H), 6.10 (1 H, br s, 4-H); ^{19}F NMR 182.6 (d, J = 49.5 Hz); IR (KBr) 1760 (COO), 1680 (CO) cm^{-1}; mass spectrum, *m/e* 346 (M$^+$). Anal. Calcd for $C_{21}H_{27}FO_3$: C, 72.81; H, 7.86. Found: C, 72.93; H, 7.97. **17-Acetoxy-6β-fluoro-4,16-androstadien-3-one (65β)**: mp 153–158 °C (ethyl acetate–hexane); ^{1}H NMR δ 1.00 (3 H, s, 13-CH_3), 1.33 (3 H, d, J = 1.5 Hz, 10-CH_3), 2.16 (3 H, s, $COCH_3$), 5.01 (1 H, dt, J = 49.5, 2.7 Hz, 6-H), 5.50 (1 H, dd, J = 3.0, 2.2 Hz, 16-H), 5.89 (1 H, d, J = 5.2 Hz, 4-H); ^{19}F NMR 165.4 (t, J = 49.5 Hz); IR (KBr) 1760 (COO), 1690 (CO) cm^{-1}; mass spectrum *m/e* 346 (M$^+$). Anal. Calcd for $C_{21}H_{27}FO_3$: C, 72.81; H, 7.86. Found: C, 72.52; H, 7.99.

Fluorination of Enol Silyl Ethers. General procedure is the same as for the fluorination of aromatics. The reaction conditions are shown in Tables XI–XIII, Scheme III, and eqs 8 and 9. Detailed procedures for **74** and **90** are described below. **16α-Fluoro-1,3,5(10)-estratrien-3-ol-17-one (70)**: ^{1}H NMR ($CDCl_3$—a few drops of DMSO-d_6) δ 0.96 (3 H, s, 13-CH_3), 5.15 (1 H, dm, J = 51.0 Hz, 16-H), 6.53–6.76 (2 H, m, 2-H, 4-H), 7.09 (1 H, d, J = 7.5 Hz, 1-H), 8.57 (1 H, s, OH); ^{19}F NMR ($CDCl_3$—a few drops of DMSO-d_6) 191.7 (m). **3-Acetoxy-16α-fluoro-3,5-androstadien-17-one (72)**: mp 155–159 °C (ethyl acetate–hexane); ^{1}H NMR δ 0.94 (3 H, s, 13-CH_3), 1.05 (3 H, s, 10-CH_3), 2.14 (3 H, s, $COCH_3$), 5.08 (1 H, dm, J = 49.5 Hz, 16-H), 5.40 (1 H, m, 6-H), 5.70 (1 H, br s, 4-H); ^{19}F NMR 191.3 (m); IR (KBr) 1750 (CO) cm^{-1}; mass spectrum, *m/e* 346 (M$^+$). Anal. Calcd for $C_{21}H_{27}FO_3$: C, 72.81; H, 7.86. Found: C, 72.67; H, 7.96. **3-Fluoro-2-dodecanone (79)**: bp 120–125 °C/20 mmHg; ^{1}H NMR δ 0.73–2.15 (15 H, m), 2.23 (3 H, d, J = 6.0 Hz, CH_3), 4.70 (1 H, dt, J = 51.0, 6.9 Hz, CHF); ^{19}F NMR 187.9 (m); IR (neat) 1725 (CO) cm^{-1}; mass spectrum, *m/e* 174 (M$^+$). Anal. Calcd for $C_{10}H_{19}FO$: C, 68.93; H, 10.98. Found: C, 68.92; H, 11.06. **Cyclohexyl 1-fluoroethyl ketone (82)**: bp 100–115 °C/30 mmHg; ^{1}H NMR δ 1.03–2.00 (10 H, m), 1.47 (3 H, dd, J = 23.4, 6.9 Hz, CH_3), 2.63–3.03 (1 H, m, CH), 4.90 (1 H, dq, J = 49.5, 6.9 Hz, CHF); ^{19}F NMR 183.7 (dq, J = 49.5, 23.4 Hz); IR (neat) 1720 (CO) cm^{-1}; mass spectrum, *m/e* 158 (M$^+$). Anal. Calcd for $C_9H_{15}FO$: C, 68.32; H, 9.55. Found: C, 68.11; H, 9.82.

Preparation of 9α-Fluoro-5β-androstan-3,11,17-trione (74). A mixture of 307 mg (1.01 mmol) of 5β-androstan-3,11,17-trione, 0.8 mL (5.7 mmol) of triethylamine, and 0.8 mL (4.14 mmol) of trimethylsilyl triflate in 10 mL of dry toluene was refluxed for 2.5 h under argon atmosphere. The reaction mixture was transferred to a dropping funnel, and the upper layer was separated from the lower layer. The upper toluene layer was washed with saturated aqueous sodium bicarbonate solution and then with water, dried with anhydrous magnesium sulfate, filtered, and evaporated to dryness to give 510 mg of **73**. The ^{1}H NMR analysis showed that **73** was contaminated with small amounts of isomeric enol

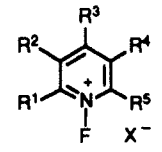
trimethylsilyl ethers, and the purity of **73** was about 85%. Tris(trimethylsilyl ether) **73** was used for the next reaction without further purification. To a solution of 510 mg (purity 85%, 0.83 mmol) of **73** in 5 mL of methylene chloride was added 210 mg (0.85 mmol) of **1**, and the mixture was stirred for 2 h under argon atmosphere at room temperature. The reaction mixture was poured into water and extracted with methylene chloride. After the extract was stirred with 10% hydrochloric acid for 1 h at room temperature, the organic layer was washed with saturated aqueous sodium bicarbonate solution and then with water, dried with anhydrous magnesium sulfate, filtered, and evaporated. The residue was column chromatographed on silica gel by using a 15:1 mixture of methylene chloride and acetonitrile as an eluent to give 140 mg (51%) of **74**, 108 mg (35%) of starting triketone, and 12 mg (4.6%) of other fluorinated steroids. **74**: mp 172–174 °C (ethyl acetate–hexane); ^{1}H NMR (400 MHz) δ 0.86 (3 H, s, 13-CH_3), 1.31 (3 H, s, 10-CH_3), 2.42 (1 H, dd, J = 12.4, 1.3 Hz, CH), 2.56 (1 H, dd, J = 19.7, 9.0 Hz, CH), 2.86 (1 H, dd, J = 12.4, 6.5 Hz, CH); ^{19}F NMR 178.9 (d, J = 28.2 Hz); ^{13}C NMR 38.30 (d, J_{F-8-C} = 21.50 Hz, 8-C), 38.85 (d, J_{F-10-C} = 18.59 Hz, 10-C), 98.96 (d, J_{C-F} = 182.7 Hz, 9-C), 204.24 (d, J_{F-11-C} = 28.7 Hz, 11-C); IR (KBr) 1710 (CO) cm^{-1}; mass spectrum, m/e 320 (M^+). Anal. Calcd for $C_{19}H_{25}FO_3$; C, 71.23; H, 7.86. Found: C, 70.98; H, 8.02.

Preparation of 4-Fluoro-2-oxa-6-*exo*-[[(*tert*-butyldimethylsilyl)oxy]-methyl]-7-*endo*-(tetrahydropyranyloxy)-*cis*-bicyclo[3.3.0]octan-3-one (90). To a solution of 1.20 mL (8.55 mmol) of diisopropylamine in 5 mL of THF cooled at 0 °C was added dropwise 4.87 mL of *n*-butyllithium–hexane (1.62 mol/L) under argon atmosphere. After stirring for an additional 15 min, the reaction mixture was cooled to −40 °C, and a solution of 2.71 g (7.30 mmol) of **89** in 7 mL of THF was added dropwise to the reaction mixture. After stirring for an additional 20 min, 1.19 mL (9.34 mmol) of chlorotrimethylsilane was added to the solution cooled at −40 °C, and the mixture was stirred for 5 min at −40 °C and then for 30 min at room temperature. The solvent was evaporated below room temperature. Under argon atmosphere, some diethyl ether was added to the residue, and the resulting precipitates were removed by filtration. The filtrate was evaporated to dryness below room temperature to give enol trimethylsilyl ether of **89** as colorless oil. The enol silyl ether was dissolved in 15 mL of methylene chloride, and the solution was added dropwise to a stirred mixture of 2.94 g (8.78 mmol) of **7** and 1.01 g (7.3 mmol) of anhydrous potassium carbonate in 10 mL of methylene chloride at room temperature. After stirring for an additional 15 min, 50 mL of saturated aqueous sodium chloride solution was added to the reaction mixture, and the mixture was extracted with diethyl ether. The extract was washed with saturated aqueous sodium chloride solution, dried with anhydrous magnesium sulfate, filtered, and evaporated. The resulting red oil was column chromatographed on silica gel by using a 9:2:0.4 mixture of hexane, diethyl ether, and methylene chloride as an eluent to give **90** in 65% overall yield as a pale yellow oil. **90**: ^{1}H NMR δ 0.06 (6 H, s, CH_3), 0.89 (9 H, s, *t*-Bu), 1.40–1.80 (6 H, m), 2.02–3.02 (4 H, m), 4.10–4.26 (1 H, m), 4.60–4.68 (1 H, br s), 5.13 (1 H, dd, J = 52, 3 Hz, CHF), 5.15 (1 H, t, J = 7 Hz); ^{19}F NMR 179.3 (dd, J = 51, 32 Hz), 179.6 (dd, J = 51, 32 Hz); IR (neat) 1790 (CO) cm^{-1}; mass spectrum, m/e 304 (M^+ − 84), millimass 304.1509 (calcd for $C_{14}H_{25}FO_4Si$, 304.1505).

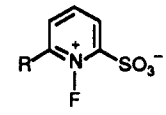
Conversion of 90 to 4-Fluoro-2-oxa-6-(hydroxymethyl)-7-*endo*-hydroxy-*cis*-bicyclo[3.3.0]octan-3-one (91). Under argon atmosphere, 4 mL of a 3:0.5:1 mixture of acetic acid, THF, and water was added to 270 mg (0.695 mmol) of **90**, and the solution was heated at 50 °C for 7 h. After 10 mL of ethyl acetate was added to it, the reaction mixture was adjusted to pH 8 with saturated aqueous sodium bicarbonate solution and extracted with ethyl acetate. The extract was washed with saturated aqueous sodium chloride solution, dried with anhydrous magnesium sulfate, filtered, and evaporated. The resulting pale yellow oil was column chromatographed on silica gel by using a 1:1 mixture of hexane and diethyl ether as an eluent to give 27.8 mg (21%) of **91** as a pale yellow oil. **91**: ^{1}H NMR ($CDCl_3$–CD_3CN) δ 2.00–2.50 (3 H, m), 2.50–3.20 (3 H, m), 3.30–3.65 (2 H, m), 4.05–4.35 (1 H, m), 5.10 (1 H, dd, J = 51, 3 Hz, CHF), 5.17 (1 H, dt, J = 6, 3 Hz); ^{19}F NMR ($CDCl_3$–CD_3CN) 179.3 (dd, J = 51, 32 Hz); IR (neat) 3400 (OH), 1780 (CO) cm^{-1}; mass spectrum, m/e 191 (M^+ + 1).

Fluorination of Enamines. Typical Procedure. A solution of 125 mg (0.5 mmol) of *N*-fluoropyridinium salt **1** in 3 mL of acetonitrile was added to a stirred solution of 180 mg (0.5 mmol) of 3-morpholino-3,5-androstadien-17β-ol (**59a**) in 3 mL of methylene chloride cooled at −15 °C under argon atmosphere. The reaction mixture was stirred for 1 h at the temperature, and then the solvent was evaporated by a rotary evaporator. Into the residue, 4 mL of *N*,*N*-dimethylformamide and 0.5 mL of concentrated hydrochloric acid were added, and the mixture was stirred for 14 h at room temperature. The reaction mixture was poured into water and extracted with methylene chloride. The extract was washed with aqueous sodium bicarbonate solution and then with water, dried with anhydrous magnesium sulfate, and filtered. The residue obtained by evaporation of solvent was thin-layer chromatographed on silica gel using a 15:1 mixture of methylene chloride and acetonitrile as an eluent to give 46% of 4-fluoro-4-androsten-17β-ol-3-one (**75**) and 15% of testosterone.

Chart I



	X	R^{1-5}
1	OTf	R^{1-5} = H
1a	$OSO_2C_4F_9^n$	R^{1-5} = H
1b	BF_4	R^{1-5} = H
1c	SbF_6	R^{1-5} = H
1d	ClO_4	R^{1-5} = H
2	OTf	$R^{1,3,5}$ = Me, $R^{2,4}$ = H
3	OTf	$R^{1,3,5}$ = H, $R^{2,4}$ = Cl
3a	BF_4	$R^{1,3,5}$ = H, $R^{2,4}$ = Cl
4	OTf	$R^{1,5}$ = COOMe, R^{2-4} = H
5	OTf	$R^{1,5}$ = Cl, R^{2-4} = H
6	OTf	R^{1-5} = Cl
7	OTf	$R^{1,5}$ = CH_2OMe, R^{2-4} = H
8	OTf	$R^{1,3,5}$ = CH_2OMe, $R^{2,4}$ = H
9	OTf	$R^{1,5}$ = CH_2OCOMe, R^{2-4} = H
10	OTf	$R^{1,2,4,5}$ = H, R^3 = *t*-Bu
11	OTf	$R^{1,5}$ = Me, R^{2-4} = H



12 R = H
13 R = Cl

Fluorination of Alkenes. Typical Procedure. To a stirred mixture of 1.26 g (3 mmol) of **6** and 6 mL of acetic acid was added 0.345 mL (3 mmol) of styrene under argon atmosphere at room temperature. Mild exothermic reaction occurred. After stirring for 30 min, the reaction mixture was poured into water and extracted with diethyl ether. The extract was washed with water and then with saturated aqueous sodium bicarbonate solution, dried with anhydrous magnesium sulfate, filtered, and evaporated. The residue was column chromatographed on silica gel by using hexane and then a 10:1 mixture of hexane and diethyl ether as eluents. The reaction conditions are shown in Table XV. Addition product **92** was obtained in 72% yield, and pentachloropyridine was recovered in 70% yield. The structural assignment of product **99** was carried out by analyses of NMR and mass spectra of the mixture, since separation of **99** from the starting alkene was difficult. **1-Acetoxy-2-fluoro-1-phenylethane (92)**: bp 190–200 °C/63–65 mmHg; ^{1}H NMR δ 2.11 (3 H, s, CH_3), 4.50 (2 H, dm, J = 48.0 Hz, CH_2), 6.03 (1 H, ddd, J = 16.8, 6.5, 4.5 Hz, CH), 7.34 (5 H, s, phenyl); ^{19}F NMR 223.8 (dt, J = 48.0, 16.8 Hz); IR (neat) 1740 (CO) cm^{-1}; mass spectrum, m/e 182 (M^+). Anal. Calcd for $C_{10}H_{11}FO_2$: C, 65.93; H, 6.09. Found: C, 65.69; H, 6.25. **2-Fluoro-1-methoxy-1-phenylethane (93)**: bp 110 °C/25 mmHg; ^{1}H NMR δ 3.30 (3 H, s, CH_3), 4.0–4.9 (3 H, m, $CHCH_2$), 7.0–7.6 (5 H, m, phenyl); ^{19}F NMR 220.5 (td, J = 49.4, 14 Hz); mass spectrum, m/e 154 (M^+). Anal. Calcd for $C_9H_{11}FO$: C, 70.11; H, 7.19. Found: C, 70.13; H, 7.26. **1-Ethoxy-2-fluoro-1-phenylethane (94)**: oil; ^{1}H NMR δ 1.20 (3H, t, J = 7 Hz, CH_3), 3.50 (2 H, q, J = 7 Hz, OCH_2), 4.0–4.8 (3 H, m, $CHCH_2$), 7.3–7.4 (5 H, m, phenyl); ^{19}F NMR 220.3 (m); mass spectrum, m/e 168 (M^+). Anal. Calcd for $C_{10}H_{13}FO$: C, 71.41; H, 7.79. Found: C, 71.44; H, 7.77. **1-Acetoxy-2-fluoro-1-phenylpropane (95)**: oil; for less polar isomer ^{1}H NMR (400 MHz) δ 1.21 (3 H, dd, J = 23.74, 6.4 Hz, methyl), 2.12 (3 H, s, $COCH_3$), 4.86 (1 H, ddq, J = 48.11, 6.4, 6.4 Hz, CHF), 5.78 (1 H, dd, J = 15.1, 6.68 Hz, CHOCO), 7.3–7.4 (5 H, m, phenyl); ^{19}F NMR 181.8 (m); for more polar isomer ^{1}H NMR (400 MHz) δ 1.29 (3 H, dd, J = 21.83, 6.4 Hz, methyl), 2.15 (3 H, s, $COCH_3$), 4.89 (1 H, dqd, J = 47.51, 3.85, 6.4 Hz, CHF), 5.83 (1 H, dd, J = 17.7, 3.85 Hz, CHOCO), 7.3–7.4 (5 H, m, phenyl); ^{19}F NMR 183.8 (m); IR (neat) (as a 1:1 mixture of threo and erythro isomers) 1740 (CO) cm^{-1}; mass spectrum (as a 1:1 mixture of threo and erythro isomers), m/e 175, 148. Anal. Calcd for $C_{11}H_{13}FO_2$: C, 67.33; H, 6.68. Found (as a 1:1 mixture of threo and erythro isomers):

Table II. Fluorination of Phenol with *N*-Fluoropyridinium Salts

salt[a]	solv	temp[b] (°C)	time (h)	conv[c] (%)	product[d] (%) 16	17	18	ratio o/p
1	$CHCl_2CH_2Cl$	100	24	75	51	18	6	2.8
2[e]	$CHCl_2CH_2Cl$	100	24	75	47	31	3	1.5
3	CH_2Cl_2	refl	5	73	60	18	7	3.3
3a	CH_2Cl_2	refl	24	63	84	10	trace	8.4
4	CH_2Cl_2	rt	18	78	30	24	3	1.3
5	CH_2Cl_2	rt	5	75	37	28	1	1.3
6	CH_2Cl_2	rt	<0.1	90	38	15	7	2.5
7	$CHCl_2CH_2Cl$	100	2	88	50	38	8	1.3
12	$CHCl_2CH_2Cl$	refl	1.5	81	55	0	0	infinity
13	$CHCl_2CH_2Cl$	100	49	95	58	0	0	infinity

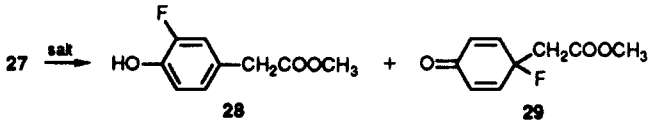
[a] An equivalent amount of salt to a substrate was used. [b] Refl = reflux temperature; rt = room temperature. [c] Determined by GLC. [d] Determined by GLC on the basis of consumed phenol. [e] Under the reaction conditions, a small amount of **2** remained.

Table III. Fluorination of Phenol Derivatives and Naphthols

run	substrate	salt[a]	solv	temp[b]	time (h)	conv[c] (%)	product (yield[d] (%))
1	methyl 4-hydroxybenzoate	**3**	$(CH_2Cl)_2$	refl	40	51	methyl 3-fluoro-4-hydroxybenzoate (53)
2	4-chlorophenol	**3**	$(CH_2Cl)_2$	refl	23	54	4-chloro-2-fluorophenol (52)
3	4-nitrophenol	**6**	CH_2Cl_2	refl	17	89	2-fluoro-4-nitrophenol (73)[f]
4	*N*,*N*-phthaloyltyrosine methyl ester (**19**)	**3**	CH_2Cl_2	refl	24	74	methyl 3-(3′-fluoro-4′-hydroxyphenyl)-2-phthalimidopropanate (**20**) (79)
5	estrone (**21**)	**2**	$(CH_2Cl)_2$	refl	18	64	2-fluorestrone (**22**) (27), 4-fluorestrone (**23**) (25)
6	**21**	**7**	CH_2Cl_2	refl	18	80	**22** (28), **23** (22)
7	methyl 4-methoxylphenylacetate (**24**)	**4**	CH_2Cl_2	refl	25	62	methyl 3-fluoro-4-methoxyphenylacetate **25** (47), **29** (31)
8	1-naphthol	**1**	CH_2Cl_2	refl	22	85	2-fluoro-1-naphthol[g] (42), 4-fluoro-1-naphthol[g] (9), 2,2-difluoro-1(2*H*)-naphthalenone[g] (5)
9	2-naphthol	**3**	CH_2Cl_2	rt	26 (0.1)[e]	80	1-fluoro-2-naphthol[g] (84), 1,1-difluoro-2(1*H*)-naphthalenone (**26**)[g] (11)

[a,b] See Table II. [c] Calculated based on the substrates recovered by column chromatography on SiO_2. [d] Isolated yields, which were calculated on the basis of consumed substrates. [e] Although the reaction mixture was stirred for 26 h, the reaction finished in 0.1 h. [f] Lerman, O.; Yitzhak, T.; Hebel, D.; Rozen, S. *J. Org. Chem.* **1984**, *49*, 806. [g] See 38a in the references.

Table IV. Fluorination of Methyl 4-Hydroxyphenylacetate (**27**)



28 **29**

run	salt[a]	solv	temp[b] (°C)	time (h)	conv[c] (%)	yield[d] (%) 28	29
1	**2**	$CHCl_2CH_2Cl$	100	54	84	44	0
2	**1**	$CHCl_2CH_2Cl$	100	30	86	41	0
3	**3**	CH_2Cl_2	refl	48	89	51	0
4	**4**	CH_2Cl_2	refl	3	79	46	23
5	**5**	CH_2Cl_2	refl	19.5	81	48	0
6	**6**	CH_2Cl_2	rt	overnight	100	42	0
7	**7**	$CHCl_2CH_2Cl$	100	1	98	40	8
8	**9**	CH_2Cl_2	refl	24	76	68	12

[a,b] See Table II. [c] Based on the recovered **27**. [d] Isolated yields which were calculated based on the consumed **27**.

C, 67.19; H, 6.78. **1-Fluoro-2-isopropoxy-2-phenylpropane (97)**: bp 140 °C/25 mmHg; ^{1}H NMR (400 MHz) δ 1.04 (3 H, d, J = 6.1 Hz, CH_3), 1.16 (3 H, d, J = 6.1 Hz, CH_3), 1.67 (3 H, d, J = 2.3 Hz, CH_3), 3.63 (1 H, septet, J = 6.1 Hz, OCH), 4.31 (1 H, dd, J = 47.4, 9.3 Hz, CHF), 4.47 (1 H, dd, J = 48.3, 9.3 Hz, CHF), 7.52–7.27 (5 H, m, phenyl); ^{19}F NMR 222.0 (t, J = 48 Hz); mass spectrum, m/e 176 (M^+ − HF). Anal. Calcd for $C_{12}H_{17}FO$: C, 73.44; H, 8.73. Found: C, 73.31; H, 73.44. **2-Acetoxy-1-fluoro-2-methylpentane (98)**: oil; ^{1}H NMR (400 MHz) δ 0.94 (3 H, t, J = 7.4 Hz, CH_2CH_3), 1.25–1.40 (2 H, m, CH_2CH_3), 1.44 (3 H, s, $-CCH_3$), 1.63–1.92 (2 H, m, EtCH_2), 2.01 (3 H, s, $COCH_3$), 4.51 (1 H, dd, J = 47.3, 9.53 Hz, CHF), 4.53 (1 H, dd, J = 47.37, 9.53 Hz, CHF); ^{19}F NMR 229.2 (t, J = 46.7 Hz); IR (neat) 1755 (CO) cm^{-1}; mass spectrum, m/e 147 (M^+ − 15). **3-Fluoro-2-methyl-5-phenyl-1-pentene (99)**: ^{1}H NMR (400 MHz) δ 1.75 (3 H, s, methyl), 1.85–2.15 (2 H, m, PhCH_2), 2.58–2.85 (2 H, m, CH_2CHF), 4.82 (1 H, ddd, J = 48.12, 8.19, 4.52 Hz, CHF), 4.95 (1 H, m, vinyl), 5.00 (1 H, d, J = 0.87 Hz, vinyl), 7.0–7.5 (5 H, m, phenyl); ^{19}F NMR 180.1 (ddd, J = 46.8, 29.6, 17.3 Hz); mass spectrum, m/e 178 (M^+), millimass 178.1131 (calcd for $C_{12}H_{15}F$, 178.1158).

Results

Of the *N*-fluoropyridinium salts synthesized in our previous study,[18] **1**, **1a–d**, **2**, **3**, **3a**, and **4–13** were used to conduct fluorination and examine the mechanisms involved. Their reactivities toward various substrates are described below.

Fluorination of Aromatics. Table I shows the controlled fluorination of a series of *N*-fluoropyridinium triflates **1–6** toward equimolar amounts of anisole in a halocarbon solvent to give *o*- and *p*-fluorinated anisoles **14** and **15**. The electrophilic fluorinating power of the triflates was found to dramatically increase in the order, **2** < **1** < **3** < **4** < **5** < **6**. It is evident that 2,4,6-trimethyl triflate **2** requires the highest temperature of 147 °C and a long reaction time for fluorination, while pentachloro triflate **6** immediately fluorinates anisole even at room temperature.

The strongest pentachloro salt **6** easily fluorinated an equimolar amount of benzene in methylene chloride solvent for 2 h at reflux temperature to give fluorobenzene in 48% ^{19}F NMR yield. It did not fluorinate methyl benzoate, a deactivated aromatic, under the same conditions. Naphthalene was more easily fluorinated by **6** (0 °C → room temperature, 45 min) to give 50% of 1-fluoronaphthalene along with a trace of the 2-fluoro isomer.[16] 2,6-Bis(methoxycarbonyl) salt **4** was heated in a benzene solution in a sealed tube in a bath at 90 °C for 24 h to give fluorobenzene in 56% ^{19}F NMR yield but failed to fluorinate an equimolar benzene in a halocarbon solvent.

Tables II and III show the fluorinations of phenol, naphthol, and their derivatives. As expected, activated aromatics such as phenol and naphthol were effectively fluorinated with mild **1**. Phenol was vigorously fluorinated by pentachloro salt **6** at room temperature giving an ca. 5:2:1 mixture of *o*-fluorophenol **16**, *p*-fluoro isomer **17**, and 2,4-difluorophenol **18**, while *p*-nitrophenol was moderately fluorinated by **6**. There was no ortho selectivity in the fluorination of anisole as shown in Table I, but phenol was preferentially fluorinated at ortho positions. Triflates **1**, **3**, and **6** gave o/p = 2.5–3.3 and tetrafluoroborate **3a**, o/p = 8.4, and counteranion-bound salts **12** and **13** brought about ortho fluorination only. Triflates **2**, **4**, **5**, and **7** showed low ortho selectivity

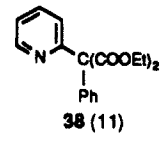
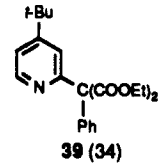
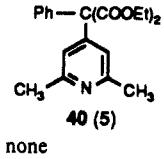
Table V. Fluorination of Aniline Derivatives

run	substrate	salt[a]	solv	temp[b] (°C)	time (h)	conv[c] (%)	product (yield[d] (%))	ratio o/p
1	acetanilide	**4**	CH_2Cl_2	refl	48	53	*o*-fluoride **30**[e] (28) *p*-fluoride **31**[f] (23)	1.2
2	acetanilide	**5**	CH_2Cl_2	refl	43	56	**30** (51), **31** (22)	2.3
3	acetanilide	**6**	CH_2Cl_2	0 → rt[n]	23	60	**30** (58), **31** (16) 2,4-difluoride **32**[g] (6)	3.6
4	phenylurethane	**3**	$(CH_2Cl)_2$	refl	5.5	62	*o*-fluoride **33**[h] (60) *p*-fluoride **34**[i] (23) 2,4-difluoride **35**[j] (6)	2.6
5	phenylurethane	**4**	CH_2Cl_2	refl	32	68	**33** (47), **34** (32), **35** (5)	1.5
6	phenylurethane	**6**	CH_2Cl_2	0 → rt[n]	5	82	**33** (53), **34** (21), **35** (13)	2.5
7	phenylurethane	**7**	$(CH_2Cl)_2$	refl	67	85	**33** (53), **34** (27), **35** (9)	2.0
8	phenylurethane	**9**	CH_2Cl_2	refl	8	82	**33** (47), **34** (29), **35** (9)	1.6
9	phenylurethane	**13**	$(CH_2Cl)_2$	refl	72	84	**33** (73), **34** (6), **35** (3)	12
10	*p*-tolylurethane	**3**	CH_2Cl_2	refl	38	56	2-fluoride[k] (71)	
11	*p*-fluorophenylurethane	**6**	CH_2Cl_2	0 → rt[n]	22	79	2,4-difluoride[l] (68)	
12	2,4-difluorophenylurethane	**6**	CH_2Cl_2	0 → rt[n]	22	74	2,4,6-trifluoride[m] (17)	

[a,b] See Table II. [c] Based on recovered substrates. [d] Isolated yields based on the consumed substrates. [e] *o*-Fluoroacetanilide. [f] *p*-Fluoroacetanilide. [g] 2,4-Difluoroacetanilide. [h] *o*-fluorophenylurethane. [i] *p*-fluorophenylurethane. [j] 2,4-Difluorophenylurethane. [k] (2-Fluoro-4-methylphenyl)urethane. [l] 2,4-Difluorophenylurethane. [m] 2,4,6-Trifluorophenylurethane. [n] The reaction mixture was stirred on an ice bath for 15–30 min and then stirred at room temperature.

Table VI. Reaction of Sodium Salt **36** of Diethyl Phenylmalonate with *N*-Fluoropyridinium Triflates

$$\underset{\mathbf{36}}{PhC^-(COOEt)_2Na^+} \xrightarrow[\text{rt, 30 min}]{\text{salt}} \underset{\mathbf{37}}{PhCF(COOEt)_2} + \text{byproduct}$$

run	salt[a]	solv	yield of **37**[b] (%)	byproduct (yield[b] (%))
1	**1**	THF	2	 **38** (11)
2	**10**	THF	8	 **39** (34)
3	**11**	THF	43	 **40** (5)
4	**2**	THF	83	none
5	**2**	DMF	85	none
6	**2**	DMSO	82	none
7	**8**	DMSO	87[c]	none

[a] See Table II. [b] Isolated yields. [c] ^{19}F NMR yield.

(o/p = 1.5–1.3). 2,4,6-Trimethyl salt **2** fluorinated estrone **21** to give a 1.1:1 mixture of the 2-fluoro isomer **22** and the 4-fluoro isomer **23** in 52% yield (run 5 in Table III). 2,6-Bis(methoxymethyl) salt **7** fluorinated **21** in better conversion yield (run 6 in Table III).

Table IV shows the fluorination of methyl *p*-hydroxyphenylacetate (**27**). Salts **4**, **7**, and **9** each having two bulky α-substituents produced *p*-fluoroquinone **29** in addition to *o*-fluoro isomer **28**, while the other salts **1**, **2**, **3**, **5**, and **6** gave **28** only. Run 7 in Table III shows the fluorination of the hydroxy-protected **24** with **4** to continue to produce a mixture of **25** and **29**, the latter being produced at a somewhat higher proportion.

It follows from the above findings that the selective ortho fluorination of the tyrosine derivative **19** occurs by 3,5-dichloro salt **3** (run 4 in Table III). As a protective group of the amino group, phthaloyl or alkoxycarbonyl functions well, while acetyl and trifluoroacetyl are not suitable. The acetyl groups appeared to decompose **3**.

Table V shows the fluorination of aniline derivatives. Salts **4**–**6** fluorinated acetanilide, while 3,5-dichloro salt **3** could not. More reactive phenylurethane was fluorinated well with **3** and more easily with **4** or **6** in better conversion yields. 2,6-Bis(acetoxymethyl) salt **9** fluorinated phenylurethane much more easily than 2,6-bis(methoxymethyl) salt **7**, thus demonstrating its greater power. The results of runs 11 and 12 clearly show that powerful pentachloro salt **6** can be used for the preparation of polyfluorinated aromatics, which so far has been difficult with known electrophilic agents.

In regard to ortho selectivity, o/p ratios in the fluorination of phenylurethane varied according to *N*-fluoropyridinium salt structure, as evident from Table V. Counteranion-bound salt **13** showed extremely high ortho selectivity, while **4**, **7**, and **9**, in which movement of the N–F moiety is rather restricted, indicated low ortho selectivity.

A heteroaromatic, 1-benzyl-2-(ethoxycarbonyl)indole, underwent fluorination with mild **2** in methylene chloride under reflux temperature for 1 day to give 1-benzyl-2-(ethoxycarbonyl)-3-fluoroindole in 60% yield (conversion yield 89%). Similarly, 2,3-dimethyl-1-phenyl-3-pyrazolin-5-one (antipyrine) was fluorinated with **2** to give 4-fluoroantipyrine[22] in 38% yield (conversion yield 87%). However, furan, pyrrole, *N*-benzylpyrrole, ethyl 2-thienylacetate, or methyl 2-thiophenecarboxylate could not be fluorinated with **2**, **1**, or **4**.

Fluorination of Carbanions. 2,4,6-Trimethyl salt **2** fluorinated *n*-dodecylmagnesium chloride at 0 °C to give *n*-dodecyl fluoride[6b] in 75% yield, while **1**, **3**, **4**, or **11** failed to do so. To determine the specificity of **2**, its reactions and those of related *N*-fluoropyridinium salts **1**, **8**, **10**, and **11** with sodium salt **36** of diethyl phenylmalonate were studied, and the results are shown in Table VI. Salt **2** and 2,4,6-tris(methoxymethyl) salt **8** each afforded only a fluoro product **37**[14a] in high yield, while **1**, **10**, and **11**, in which the α- and/or γ-positions of the pyridine ring are not substituted, gave byproducts **38**, **39**, and **40**, respectively. This shows that the specific effectiveness of **2** may possibly arise from the blocking effect of the α- and γ-positions by three methyl groups rather than the mildness of **2**.

In Table VII are given examples of the fluorination of carbanions with **2**. Salt **2** fluorinated alkyl or aryl Grignard reagents but not the corresponding organolithium compounds. The sodium salts of various active methylene compounds were fluorinated well as can be seen from Table VII. It is of interest that the sodium salt of diethyl fluoromalonate, on treatment with **2**, gave diethyl difluoromalonate in low yield, while the corresponding chloromalonate salt was fluorinated well to give the chlorofluoromalonate ester in high yield (run 9).

Lewis Acid-Catalyzed Fluorination of Active Methylene Compounds. Lewis acids accelerated the slow fluorination rates of active methylene compounds themselves with 2,4,6-trimethyl salt **2**. While treatment of ethyl oxocyclopentanonecarboxylate (**42**) with 1 equiv of **2** in 1,2-dichloroethane solvent at 60 °C for 48 h gave only a 31% yield of the fluoro product **41**[22] along with a

Table VII. Fluorination of Carbanions with *N*-Fluoro-2,4,6-trimethylpyridinium Triflate (**2**)

run	carbanion[a]	solv	temp[b] (°C)	time (h)	product	yield[c] (%)
1	n-$C_{12}H_{25}MgCl$	Et_2O	0	0.5	n-$C_{12}H_{25}F$	75
2	PhMgCl	THF	0	0.5	PhF	58
3	$CH_2(CH_2)_2COC^-COOEtNa^+$	THF	0 → rt	0.3	$CH_2(CH_2)_2COCFCOOEt$ (41)[f]	86
4[d]	$Na^+{}^-CH(COOEt)_2$	THF	0	0.1	$FCH(COOEt)_2$	73
5	$Na^+MeC^-(COOEt)_2$	THF	0	0.2	$MeCF(COOEt)_2$[g]	78
6	$CH_2COC^-(CH_3)COCH_2Na^+$	THF	rt	1	$CH_2COCF(CH_3)COCH_2$	44
7	$Na^+PhC^-(CN)_2$	THF	0 → rt	0.2	$PhCF(CN)_2$	71
8[e]	$Na^+PhSO_2C^-HCOOEt$	THF	0	0.2	$PhSO_2CFHCOOEt$	49
					$PhSO_2CF_2COOEt$	4
9	$Na^+ClC^-(COOEt)_2$	THF	0	0.2	$ClCF(COOEt)_2$	86

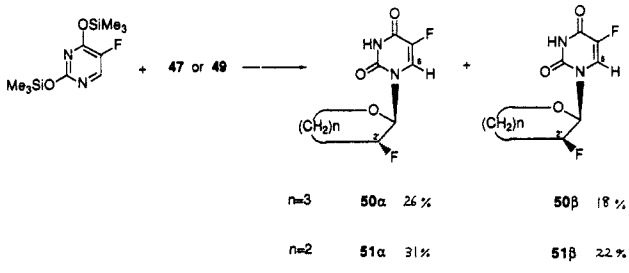
[a] An equivalent amount of a carbanion to **2** was used except for run 3 where 0.91 equiv amount of the carbanion was used. [b] See in Table II. [c] Isolated yields except for run 1 (GLC yield) and run 2 (^{19}F NMR yield). The yields were calculated based on the used amounts of substrates. [d] A small amount of diethyl difluoromalonate was detected as another product. [e] $PhSO_2CH_2COOEt$ was recovered in 41% yield. [f] See ref 23. [g] See ref 14a.

Table VIII. Lewis Acid-Catalyzed Fluorination of Active Methylene Compounds with *N*-Fluoro-2,4,6-trimethylpyridinium Triflate (**2**)

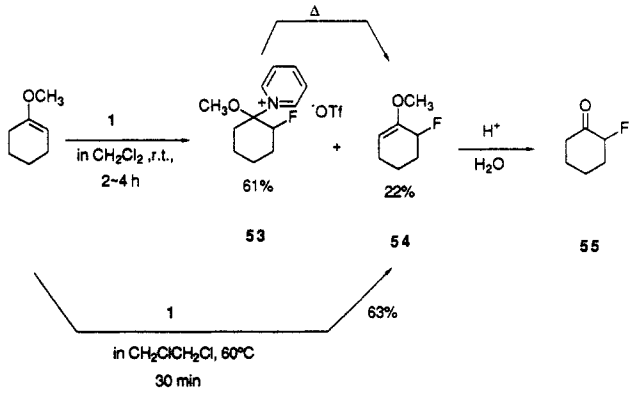
run[a]	substrate	equiv of **2**[b]	Lewis acid (equiv)[b]	temp (°C)	time (h)	product	yield[c] (%)
1[d]	**42**	1	$ZnCl_2$ (0.4)	60	18	**41**	67
2	$CH_2(COPh)_2$ **43**	2	$ZnCl_2$ (0.4)	60	18	$CF_2(COPh)_2$ **44**	88
3	CH_3COCH_2COOEt	1	$ZnCl_2$ (0.4)	60	24	$CH_3COCFHCOOEt$[e]	69
						CH_3COCF_2COOEt	12
4	CH_3COCH_2COOEt	2	$ZnCl_2$ (0.4)	60	12	$CH_3COCFHCOOEt$[e]	32
						CH_3COCF_2COOEt	64
5[d]	$CH_2(COOEt)_2$	1	$ZnCl_2$ (0.4)	60	24	$CFH(COOEt)_2$	38
6[d]	$CH_2(COOEt)_2$	2	$ZnCl_2$ (0.4)	60	48	$CFH(COOEt)_2$	80
7[d]	$CH_2(COOEt)_2$	2	$AlCl_3$ (0.4)	80	24	$CFH(COOEt)_2$	19
						$CF_2(COOEt)_2$[f]	76

[a] CH_2ClCH_2Cl was used as a solvent. [b] Equivalency to the substrates. [c] ^{19}F-NMR yields except for run 2 (isolated yield). They were calculated based on the used amounts of the substrates. [d] The ^{19}F-NMR spectra of the resulting reaction mixtures showed that 0.19, 0.63, 1.04, and 0.25 equivalent amounts of **2** remained intact in run 1, 5, 6, and 7, respectively. [e] See ref 23. [f] See ref 41.

Scheme I



Scheme II



41% recovery of **2**, the addition of 0.4 equiv of zinc chloride gave 67% of the product **41** even after 18 h with 19% recovery of **2**.

$$\underset{\textbf{42}}{CH_2CH_2CH_2COCH(COOEt)} \rightleftarrows CH_2CH_2CH_2C(OH)=C(COOEt) \xrightarrow{\textbf{2, Lewis acid}} \textbf{41} \quad (1)$$

Table VIII summarizes the results of $ZnCl_2$- and $AlCl_3$-catalyzed fluorination with **2**. In the case of the $ZnCl_2$ catalyst, β-diketone **43** was treated with 2 equiv of **2** to produce difluoro product **44** in 88% yield (run 2), while diethyl malonate gave only the monofluoro product (80%) even when treated with 2 equiv of **2** (run 6). In the latter reaction, 1.04 equiv of **2** remained. The β-keto ester yielded a 1:2 mixture of mono- and difluoro products (run 4). The strong Lewis acid $AlCl_3$ was capable of difluorinating the malonate. A 76% yield of the difluoromalonate (run 7) was thus possible. This product has been difficult to obtain by the anion method mentioned above.

Equation 2 shows the more reactive 3,5-dichloro salt **3** to smoothly fluorinate the β-diketone **43** in the absence of a Lewis acid. However, the even more powerful 2,6-dichloro salt **5** could not fluorinate the malonate without a Lewis acid.

$$\textbf{43} \xrightarrow[\text{in } CH_2ClCH_2Cl,\ 60\ °C,\ 5\ h]{\textbf{3 (1 equiv)}} PhCOCHFCOPh + \underset{\textbf{45}}{\textbf{44}} \quad (2)$$

Fluorination of Enol Alkyl Ethers. In eq 3, **1** reacts with dihydropyran **46** in methylene chloride at reflux temperature to give the addition product **47** in 86% yield. This product was an ca. 1:1 mixture of trans and cis isomers. Dihydrofuran **48** was successfully fluorinated in the presence of a catalytic amount of pyridine (2 mol %) to give a similar addition product, **49**, in 73% yield (eq 4).

$$\underset{\textbf{46 (1.4 equiv)}}{CH_2CH_2CH_2CH=CH} \xrightarrow[\text{in } CH_2Cl_2,\ \text{reflux, 7 h}]{\textbf{1}} \underset{\textbf{47 (86\%)}}{CH_2CH_2CH_2CHFCHN^+C_5H_5{}^-OTf} \quad (3)$$

$$\underset{\textbf{48 (1.2 equiv)}}{CH_2CH_2CH=CH} \xrightarrow[\text{pyridine (2 mol \%)}]{\textbf{1, in } CH_2Cl_2,\ \text{reflux, 8 h}} \underset{\textbf{49 (73\%)}}{CH_2CH_2CHFCHN^+C_5H_5{}^-OTf} \quad (4)$$

(22) Hesse, R. H. *Isr. J. Chem.* **1978**, *17*, 60.

Table IX. Fluorination of 1-Cyclohexenyl Acetate (**76**) with *N*-Fluoropyridinium Triflates

run	salt[a]	solv.	temp[b] (°C)	time (h)	yield of **55** (%)[c]
1	**1**	CH_3CN	refl	14	30
2[d]	**2**	CH_3CN	refl	24	<20
3	**7**	$(CH_2Cl)_2$	refl	5	73

[a,b] See Table II. [c] ^{19}F-NMR yields based on the used amount of **67**. [d] The reaction did not finish.

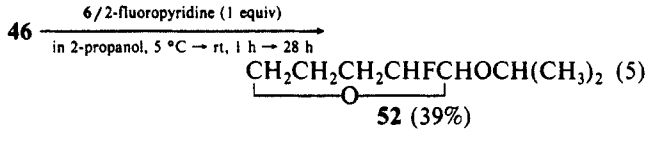
Table X. Stereoselective Fluorination of Steroid **57** with *N*-Fluoropyridinium Salts

run	salt[a]	solv	temp[b]	time (h)	yield[c] (%) **61α** + **61β**	ratio **61α**/**61β**
1	**1**	CH_2Cl_2	refl	16	72	1/2
2	**2**	CH_2Cl_2	refl	46	55	1/8.5
3	**7**	CH_2Cl_2	rt	52	52	1/7

[a] An equivalent amount of salt to **57** was used. [b] See Table II. [c] Isolated yields.

Pyridine appeared to have the role of protecting acid-labile dihydrofuran, since in its absence a dark reaction mixture was obtained, but **1** remained. Since **47** and **49** could not be obtained in pure form due to their oily quality, they were converted to 5-fluorouracil derivatives **50α**, **50β**, **51α**, and **51β** which were completely characterized. The α- or β-configuration assignment of the fluorine atom was determined from the coupling constant of 6-H and 2'-F. Coupling constant 1.5 Hz was observed in **50β** and **51β**, while the corresponding coupling in **50α** and **51α** could not be observed.

Dihydropyran **46** reacted with the strongest pentachloro salt **6** in 2-propanol solvent in the presence of 1 equiv of 2-fluoropyridine as an acid trap, giving a 1.5:1 mixture of trans and cis or cis and trans isomers of the solvent addition product **52** in 39% yield, as shown in eq 5.

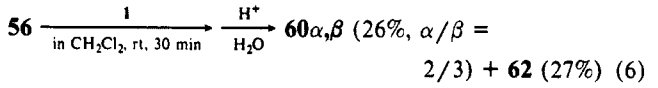


52 (39%) (5)

Scheme II shows 1-methoxy-1-cyclohexene, a different type of enol alkyl ether, to react smoothly with **1** at room temperature to give two products in 22 and 61% yields, as determined by ^{19}F NMR of the reaction mixture.

The minor product was assigned as allyl fluoride derivative **54** by spectral analysis of the isolated product. The major product with a signal at 195 ppm in the ^{19}F NMR was converted to the minor product **54** by heating and thus tentatively assigned as the addition product **53**. This reaction at elevated temperature directly gave **54** alone in 63% yield, which subsequently was easily acid-hydrolyzed to give α-fluoroketone **55**.[5b]

Conjugated enol ether **56**, derived from the corresponding α,β-unsaturated keto steroid, gave a 1:1 mixture of 6- and 4-fluoro steroids **60** and **62** (eq 6). Product **60** was a 2:3 mixture of 6α- and 6β-isomers **60α** and **60β**; **62** was a stereoisomer but whose configuration was not determined. In this reaction, 16% of the starting α,β-unsaturated keto steroid was recovered.



2/3) + **62** (27%) (6)

Fluorination of Vinyl Esters. Table IX shows the fluorination of 1-cyclohexenyl acetate (**76**) with **1**, **2**, and **7**, to give 2-fluoroketone **55**. Salt **1** did not react with this compound at 40 °C and decomposed at elevated temperature. Salt **2** was too weak to fluorinate **76** and trended to decompose at high temperature. The instability may possibly have been due to the acidic α-protons or acidic α-methyl protons of these salts. A certain amount of 2-(fluoromethyl)-4,6-dimethylpyridine, a decomposition product from **2**,[18] could actually be detected in the ^{19}F NMR spectrum of the reaction mixture. It was anticipated that 2,6-bis(methoxymethyl) salt **7** would have sufficient stability and fluorinating power since the methoxy-substituted α-methyl protons should be difficult to be deprotonated and the electron-withdrawing methoxy group should enhance the reactivity. Salt **7** was found to smoothly react with **76** to give fluoroketone **55** in good yield (run 3, Table IX). The stronger *N*-fluoropyridinium salts were not suitable for the preparation of the acid-labile α-fluoroketones since they caused the reaction mixture to become strongly acidic.

In Table X, however, a conjugated vinyl acetate **57** smoothly reacts with **1** under mild conditions to give an ca. 1:2 mixture of 6α- and 6β-fluoro steroids **61α**[24] and **61β**[24] in 72% total yield. The regioselectivity of 6β-fluorination increased with the bulkiness of the *N*-fluoropyridinium salt used. Bulky 2,4,6-trimethyl salt **2** and 2,6-bis(methoxymethyl) salt **7** produced **61β** with high stereoselectivity as shown in Table X.

Chart II

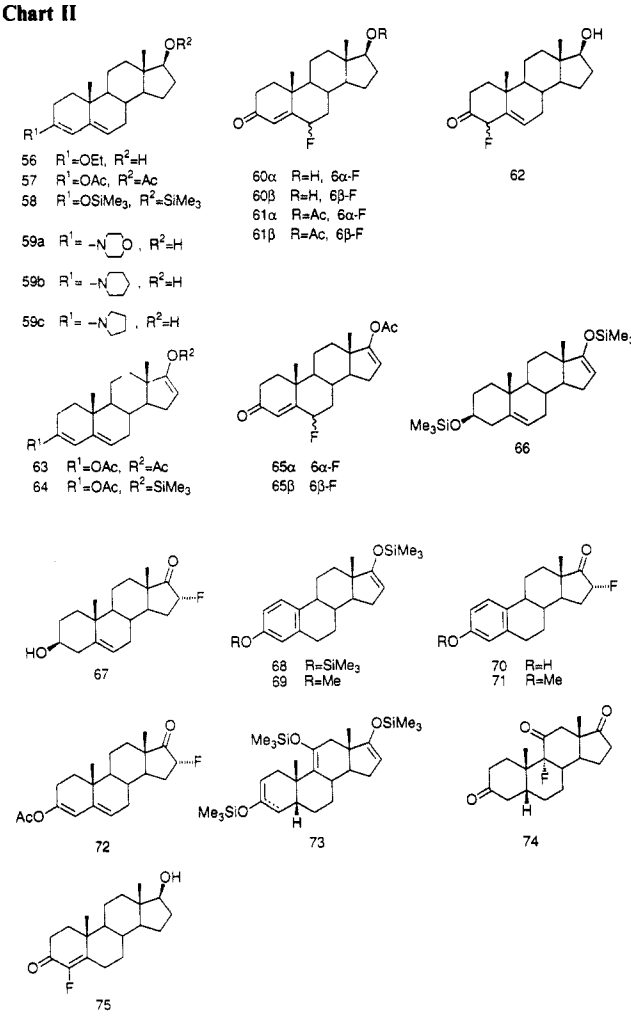


Table XI. Fluorination of 1-(Trimethylsiloxy)cyclohexene (**77**) with *N*-Fluoropyridinium Salts Having Different Counteranions in Different Solvents

run	salt[a]	solv	temp[b]	time (h)	yield of **55** (%)
1	**1**	CH_2Cl_2	rt	7	87[c]
2	**1**	CH_3CN	rt	15	83[d]
3	**1**	THF	rt	24	0[d,e]
4	**1a**	CH_2Cl_2	rt	5	69[c]
5	**1b**	CH_2Cl_2	rt	72	trace[c]
6	**1b**	CH_2Cl_2	refl	6	41[c]
7	**1b**	CH_3CN	rt	15	54[d]
8	**1c**	CH_2Cl_2	refl	8	23[c]
9	**1c**	CH_3CN	rt	20	80[d]
10	**1d**	CH_2Cl_2	refl	19	0[c,e]
11	**1d**	CH_3CN	rt	20	83[d]

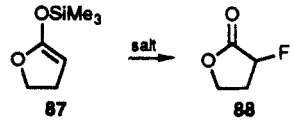
[a,b] See Table II. [c] GLC yields based on the used amount of **77**. [d] ^{19}F-NMR yields based on the used amount of **77**. [e] No reaction occurred.

Table XII. Fluorination of Enol Silyl Ethers with *N*-Fluoropyridinium Triflate (**1**)

run	enol silyl ether[a]	solv	temp[b]	time (h)	product (yield[c] (%))
1	$CH_3(CH_2)_6C(OSiMe_3)=CH_2$ **78**	CH_2Cl_2	refl	3	$CH_3(CH_2)_5CHFCOCH_3$ **79** (42)
2	$CH_3(CH_2)_5CH=C(OSiMe_3)CH_3$ **80**	CH_2Cl_2	refl	3	**79** (58)
3	c-$C_6H_{11}C(OSiMe_3)=CHCH_3$ **81**	CH_2Cl_2	refl	10	c-$C_6H_{11}COCHFCH_3$ **82** (61)
4[d]	**58**	CH_2Cl_2	rt	1	**60**α (10), **60**β (31), **62** (18)
5	**64**	CH_2Cl_2	refl	1	**72** (54)
6[d]	**66**	CH_2Cl_2	refl	1	**67**[e] (43)
7[d]	**68**	CH_2Cl_2	refl	1	**70** (50)
8	**69**	CH_2Cl_2	rt	16	**71** (78)
9[d]	**73**	CH_2Cl_2	rt	2	**74** (51)

[a] An equivalent amount of an enol silyl ether to **1** was used. [b] See Table II. [c] Isolated yields. [d] Acid hydrolysis was carried out after fluorination. [e] See ref 6b.

Table XIII. Fluorination of 4,5-Dihydro-2-(trimethylsiloxy)furan (**87**)

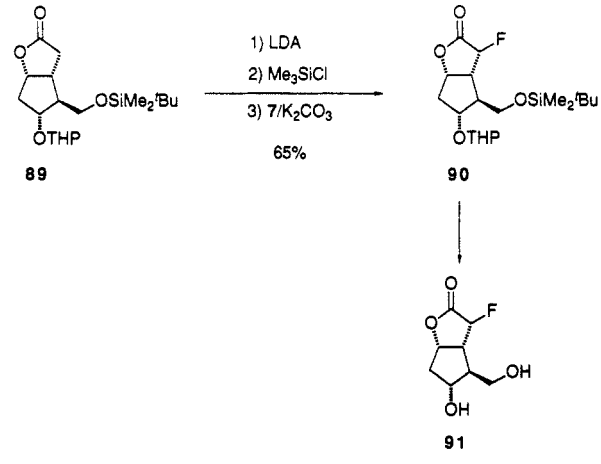


87 **88**

run	salt[a]	base[b]	solv	temp[c]	time (h)	yield of **88**[d] (%)
1	**2**	2 equiv	CH_2Cl_2	rt	ca. 12	30–40
2	**7**	none	CH_2Cl_2	rt	3	50
3	**7**	2 equiv	CH_2Cl_2	rt	5	70–80

[a] See Table II. [b] 2,6-Di-*tert*-butylpyridine was used as a base. [c] See *b* in Table II. [d] ^{19}F-NMR yields based on the used amount of **87**.

Scheme III



89 **90** **91**

In eq 7, steroid **63**, having two reactive conjugated and nonconjugated vinyl acetate moieties, was treated with 1 equiv of **1**, to give 6-fluoro isomers **65**α and **65**β through reaction with the former moiety only, judging from the marked difference between **76** and **57**.

$$\mathbf{63} \xrightarrow[\text{in } CH_2Cl_2,\ \text{reflux, 14 h}]{\mathbf{1}} \mathbf{65}\alpha,\beta\ (51\%,\ \alpha/\beta = 1/2) \qquad (7)$$

Fluorination of Enol Silyl Ethers. Enol trimethylsilyl ether **77** of cyclohexanone reacted smoothly with **1** in methylene chloride at room temperature to give α-fluoroketone **55** in good ^{19}F-NMR yields. The reaction rates depended on fluorinating power. Powerful **3** reacted in only less than 2 h, while **1** and **2** required 7 and 10 h, respectively.

In this fluorination, counteranion and solvent effects were examined by using *N*-fluoropyridinium salts having different counteranions. The results are summarized in Table XI. Triflate **1** reacted smoothly with **77** in methylene chloride while **1** failed to do so in tetrahydrofuran (THF) even after 24 h. In methylene chloride, nonafluorobutanesulfonate **1a** reacted essentially the same as triflate **1**, but tetrafluoroborate **1b**, hexafluoroantimonate **1c**, and perchlorate **1d** reacted only very slightly or not at all. But in acetonitrile **1** and **1b–d** all reacted at nearly the same rates, giving product **55** in almost the same good yields. The reaction time (15–20 h) in each case, however, was longer than that (7 h) of triflate **1** in methylene chloride. Thus, the apparent reactivity of *N*-fluoropyridinium salts varied depending on their counteranions and solvents used.

Table XIV. Fluorination of Enamines **59a–c** with *N*-Fluoropyridinium Salts

$$\mathbf{59a\text{–}c} \xrightarrow[\text{in } CH_2Cl_2\text{–}CH_3CN,\ -15\ ^\circ C]{\text{salt}} \xrightarrow[H_2O]{H^+} \mathbf{75}$$

run	enamine[a]	salt	yield (%) of **75**[b]
1	**59a**	**1**	46
2	**59a**	**2**	54
3	**59b**	**1**	22
4	**59b**	**2**	31
5	**59c**	**1**	7
6	**59c**	**2**	13

[a] An equivalent amount of salt to an enamine was used. [b] Isolated yields.

Reactive conjugated enol silyl ether **58** reacted with **1** more quickly than nonconjugated **77**. Yields of products 6α-, 6β-, and 4-fluoro steroids **60**α, **60**β, and **62** were 10, 31, and 18%, respectively (run 4 in Table XII). 4-Fluoro isomer **62** was a stereoisomer, but no determination was made of its configuration.

Triflate **1** could be effectively used for the regioselective fluorination of the enol silyl ether portion of steroids possessing other potentially reactive sites. As evident from Table XII, **1** reacted exclusively at the enol silyl ether moieties of steroids **64**, **66**, **68**, and **69** which possessed other moieties such as an activated conjugated vinyl ester, a double bond, an activated aromatic ring, a hydroxyl group, or the equivalent in one molecule.

The obtained 16α-fluoro steroid **71**[25] was shown to be contaminated by a small amount of 16β-fluoro isomer by 400-MHz ^{1}H-NMR analysis. In this reaction, 11% of the starting keto steroid was recovered, and 12% of 2-pyridyl triflate, a decomposition product[26] of **1**, was obtained.

The reaction of an acyclic terminal enol silyl ether **78** with **1** gave an unexpected product, a rearrangement fluoro product, **79**, in 42% yield, the same as that from the isomeric internal enol silyl ether **80**, which gave **79** in 58% yield, as shown in Table XII. But, an internal enol silyl ether **81** gave the expected product **82** not a rearrangement product. The NMR spectrum of the reaction mixture obtained by the reaction of **1** with 2 equiv of the terminal silyl ether **78** in deuteriomethylene chloride indicated internal silyl ether **80** to be formed in the reaction mixture, and thus there is the possibility that inactive terminal **78** isomerized to the thermally stable but reactive internal **80**, which gave the rearrangement product **79**. Reactive **81** was fluorinated by **1** before isomerizing to the corresponding trisubstitued enol silyl ether.

As shown in run 9 in Table XII, **73**, having one trialkylated and two dialkylated enol silyl ether moieties in the same molecule and prepared from the corresponding triketo steroid, was treated with 1 equiv of **1** to give almost exclusively 9α-fluoro steroid **74** in 51% yield (78% based on recovered starting triketo steroid). The combined yield of the other fluorinated products was only 4.6%. Thus by **1**, the trialkylated moiety can be clearly distin-

(23) Lerman, O.; Rozen, S. *J. Org. Chem.* **1983**, *48*, 724.
(24) Hesse, R. H. *Isr. J. Chem.* **1978**, *17*, 60.
(25) Patrick, T. B.; Mortezania, R. *J. Org. Chem.* **1988**, *53*, 5153.
(26) Umemoto, T.; Tomizawa, G. *Tetrahedron Lett.* **1987**, *28*, 2705.

Table XV. Reactions of Alkenes with *N*-Fluoropentachloropyridinium Triflate (**6**)

run	alkene[a]	base[b]	solv	temp[c]	time	product	yield[d] (%)
1	$PhCH{=}CH_2$	none	AcOH	rt	1 h	$PhCH(OAc)CH_2F$ **92**	72
2	$PhCH{=}CH_2$	none	$AcOSiMe_3$	rt	3 days	**92**	56
3	$PhCH{=}CH_2$	none	$MeOSiMe_3$	rt	5 days	$PhCH(OMe)CH_2F$ **93**	54
4	$PhCH{=}CH_2$	none	$EtOSiMe_3$	rt	18 days	$PhCH(OEt)CH_2F$ **94**	29
5	$PhCH{=}CHCH_3$ (trans)	none	AcOH	rt	20 min	$PhCH(OAc)CHFCH_3$ **95** (threo/erythro = 1)	80
6	$PhCH{=}CHCH_3$ (trans/cis = 1)	none	AcOH	rt	1 h	**95** (threo/erythro = 1)	80
7	$PhC(CH_3){=}CH_2$	none	AcOH	rt	5 min	$PhC(CH_2F){=}CH_2$ **96**	25[e]
8	$PhC(CH_3){=}CH_2$	none	Me_2CHOH	rt	10 min	$PhC(CH_3)(OCHMe_2)CH_2F$ **97**	70[e]
9	$PhC(CH_3){=}CH_2$	A	CH_2Cl_2	rt	5 min	**96**	73[e]
10	$Me(CH_2)_2C(CH_3){=}CH_2$	A	AcOH	rt	30 min	$Me(CH_2)_2C(CH_3)(OAc)CH_2F$ **98**	28
11	$Me_2C{=}CH(CH_2)_2Ph$	B	THF	rt	10 min	$CH_2{=}(CH_3)CCFH(CH_2)_2Ph$ **99**	57

[a] An equivalent amount of **6** to a substrate was used. [b] A = 2-fluoropyridine. B = 2,6-di-*tert*-butylpyridine. An equivalent amount of the base was used. [c] See *b* in Table II. [d] Isolated yields, unless otherwise noted. The yields were calculated based on the used amounts of alkenes. [e] ^{19}F-NMR yields.

guished from the two dialkylated moieties. The reaction of **73** with bulky 2,4,6-trimethyl salt **2**, however, did not produce **74**.

Ketene monosilyl acetal **83** and disilyl acetal **85** reacted smoothly with **1** or **2** to give α-fluoro ester **84**[5b] and α-fluoro carboxylic acid **86**[5b] in good yields. Acid **86** was isolated as a methyl ester in 68% yield following treatment with diazomethane.

$$\underset{\mathbf{83}}{PhCH{=}C(OEt)(OSiMe_3)} \xrightarrow[1,\,2]{\text{in } CH_2Cl_2,\ rt,\ 2\ h} \underset{\mathbf{84}\ (65\%,\ 71\%)}{PhCHFCOOEt} \quad (8)$$

$$\underset{\mathbf{85}}{PhCH{=}C(OSiMe_3)_2} \xrightarrow[2]{\text{in } CH_2Cl_2,\ rt,\ 2\ h} \underset{\mathbf{86}\ (68\%)}{PhCHFCOOH} \quad (9)$$

However, cyclic ketene silyl acetal **87** derived from γ-lactone led to different results as shown in Table XIII. A high yield of the expected α-fluoro lactone **88**[27] was obtained following its reaction with 2,6-bis(methoxymethyl) salt **7** in the presence of two equimolar amounts of 2,6-di-*tert*-butylpyridine as a neutralizing agent (run 3). This technique using **7** is a useful method for preparing α-fluoro analogue **90** of the Corey lactone **89**,[28] an important synthetic intermediate for prostaglandins[3d] (Scheme III). Lactone **89** was converted to a ketene silyl acetal, which was then treated with **7** in the presence of potassium carbonate as the neutralizing agent to give fluoro lactone **90** in 65% overall yield. The resulting lactone **90** was found to be a stereoisomer by NMR analysis of the derived **91**, but the configuration at the fluorine atom was not determined.

Fluorination of Enamines. Emanies **59a–c** were fluorinated with mild **1** or **2** at low temperature and hydrolyzed, giving 4-fluoro product **75**[29] only in different yields. As seen in Table XIV, the yields varied greatly according to the enamine used. The best yields were obtained with morpholine enamine **59a** and **2** in combination.

Fluorination of Alkenes. The most powerful **6** has sufficient reactivity to fluorinate alkenes, while mild **1** or others do not. As shown in Table XV, styrene was easily fluorinated by **6** in acetic acid at room temperature to give the fluoro acetoxy addition product **92** in 72% yield (run 1). *trans*-β-Methylstyrene and a 1:1 mixture of *trans*- and *cis*-β-methylstyrene gave the same 1:1 mixture of threo and erythro adducts **95** in the same yields (runs 5 and 6). The same treatment of α-methylstyrene did not give the corresponding addition product but α-fluoromethylstyrene (**96**)[30] in 25% yield (run 7). The use of 2-propanol as a more nucleophilic solvent gave adduct **97** in 70% yield (run 8). The elimination product **96** was obtained in good yield by reaction in a nonnucleophilic solvent such as methylene chloride in the presence of 2-fluoropyridine as an acid trap (run 9). 2-Methyl-1-pentene was fluorinated in acetic acid in the presence of 2-fluoropyridine to give adduct **98** in 28% yield (run 10). The fluorination of 1- and 2-octene under various conditions was attempted but without success. A multisubstituted ethylene, 4-methyl-1-phenyl-3-pentene, was smoothly fluorinated by **6** in THF in the presence of 2,6-di-*tert*-butylpyridine as an acid trap to give allyl fluoride derivative **99** in good yield (run 11). Although methanol and ethanol are unsuitable as solvents since they decomposed **6**, their trimethylsilyl ether solvents provided the corresponding addition products **93** and **94** in moderate yields (runs 3 and 4).

Discussion

Fluorinating Power. The controlled fluorination of a series of *N*-fluoropyridinium triflates clearly showed variation in fluorinating power due to the electronic nature of the substituents on the ring. The power of fluorination increased as the electron density of the positive nitrogen sites decreased, this being correlated to the pK_a values of the corresponding pyridines. The results of the N–F ^{19}F NMR analyses in the previous study[18] showed N–F chemical shifts to be correlated to pK_a values except in the case of α-substituents containing a heteroatom(s).

Fluorinating power also changed according to substituents on α-methyl groups. 2,6-Bis(acetoxymethyl) salt **9** having an acetoxy substituent on the α-methyl was stronger than 2,6-bis(methoxymethyl) salt **7** having a methoxy substituent, as indicated in Tables IV and V. It is thus evident that activation occurs via σ-bonds, which is in accordance with variation in the pK_a values of pyridines.

The most electron poor N–F salt **6** can fluorinate olefins or nonactivated aromatics such as benzene, while salts with relatively more electron density were unable or could do so only with difficulty. Salt **2** with the greatest electron density fluorinated easily oxidizable heteroaromatics such as the indole derivative and antipyrine and enamines **59**, giving fluorinated products in better yields, while with salts with poorer electron density, tar product quantities were greater. Electron-rich *N*-benzylpyrrole could no longer be fluorinated even by **2** but gave only tars.

As seen from Table XI, the power of a *N*-fluoropyridinium salt also varied according to the solvent used. While a nonpolar solvent such as methylene chloride increased this power, a polar solvent such as acetonitrile considerably lessened the fluorination rate of **1**. THF as a strongly coordinating solvent completely inhibited fluorination. This was due to the effective positive charge at the N–F moiety induced by solvent molecules surrounding the positive nitrogen site.

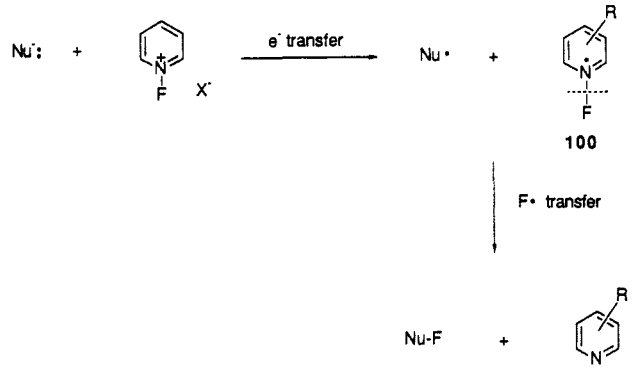
Table XI gives information on the effects of counteranions. In methylene chloride, ^-OTf showed markedly high reactivity compared with other counteranions and smoothly fluorinated **77** at room temperature. $^-BF_4$, $^-SbF_6$, and $^-ClO_4$ were essentially unable to do so. The relative higher solubility of **1**(^-OTf) may be the reason for this, since the reactivity of counteranions in acetonitrile, which freely or sufficiently dissolve the salts **1**, **1a–d**, was essentially the same. However, as suggested from the solvent effects discussed above, the great reactivity of ^-OTf in a nonpolar solvent may partly

(27) Partridge, J. J. *Abstracts of Papers*; 188th National Meeting of the American Chemical Society, Philadelphia, PA, August 26–31, 1984; American Chemical Society: Washington, DC, 1984; MEDI 1.

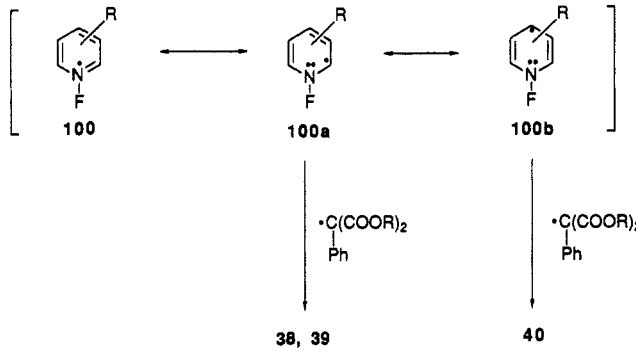
(28) (a) Corey, E. J.; Schaaf, T. K.; Huber, W.; Koelliker, U.; Weinschenker, N. M. *J. Am. Chem. Soc.* **1970**, *92*, 397. (b) Corey, E. J.; Noyori, R.; Schaaf, T. K. *Ibid.* **1970**, *92*, 2586.

(29) Nakanishi, S. *Steroids* **1963**, *2*, 765; **1964**, *3*, 337.

Scheme IV



Scheme V



be attributed to the nature of $^{-}$OTf, a completely delocalized bulky anion incapable of neutralizing the positive charge of the N–F moiety as effectively as other counteranions.

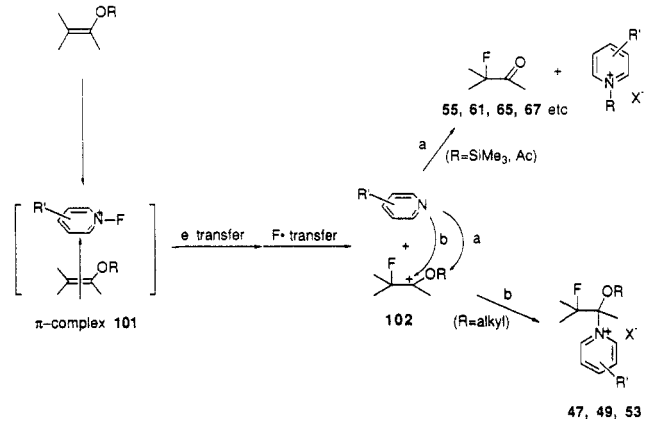
Reaction Mechanism. *N*-Fluoropyridinium salts appeared to provide positive fluorine (F^{+} or $F^{\delta+}$) in fluorination reactions. However, this should not be the case in consideration of the extremely high ionization potential of a fluorine atom[31] and the high-electron affinity of greatly electron-deficient pyridinium ring system. As discussed below, all fluorinations by *N*-fluoropyridinium salts can be explained well by a one-electron-transfer mechanism. As shown in Scheme IV, in the fluorination of a carbanion, one electron transfers from the carbanion (Nu:$^{-}$) to a *N*-fluoropyridinium moiety, followed by homolytic fission of the N–F bond of **100** and the combining of F• with Nu•.

This mechanism appeared to be supported by the observed great difference between organolithiums and magnesium halides: the latter Grignard reagents gave the corresponding fluoro products, while the former did not. This is because reactions of Grignard reagents have been shown to each involve a one-electron transfer.[32] This mechanism would also clearly explain that, although **2** has acidic 2,6-dimethyl protons as demonstrated in the previous paper,[18] 2,4,6-trimethyl salt **2** fluorinated carbanions in good yields. The deprotonation of **2** by carbanions should not give the expected fluoroproducts. Byproducts **38**, **39**, and **40** may be explained by the one-electron-transfer mechansim, as seen in Scheme V. This mechanism may also explain the formation of 2-(trinitromethyl)pyridine by treatment of *N*-fluoropyridinium fluoride[18] with trinitromethane.[33]

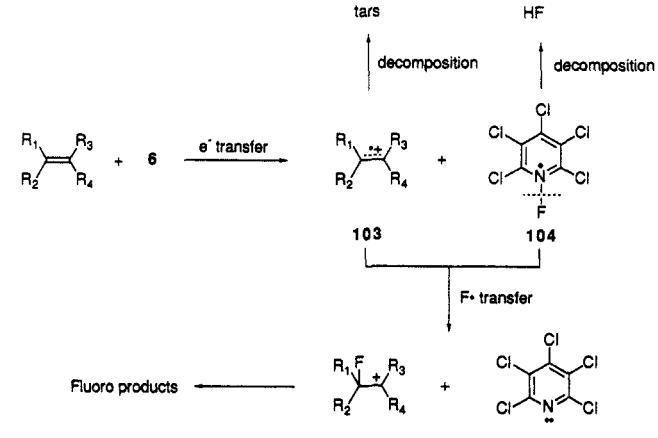
The fluorination of nonionic substrates by *N*-fluoropyridinium salts may result by a similar one-electron-transfer mechanism through the π-complex. The formation of this complex between an electron-deficient *N*-fluoropyridinium salt and an electron-rich substrate would likely occur. In fact, for example, on mixing **3**

(30) Baldwin, M. G.; Reed, S. F., Jr. *J. Polym. Sci.* **1968**, *6*, 2627.
(31) Sheppard, W. A.; Sharts, C. M. *Organic Fluorine Chemistry*; W. A. Benjamin, Inc.: New York, 1969; p 11.
(32) (a) Cowley, D. J. *Organic Reaction Mechanism 1985*; Knipe, A. C., Watts, W. E., Eds.; John Wiley & Sons Ltd.: New York, 1987; pp 144–145. (b) Okubo, M. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 2057. (c) Okubo, M. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 3108.
(33) Gakhand, A. A.; Khutoretskii, V. M. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1983**, 2655; *Chem. Abstr.* 100-85558u.

Scheme VI



Scheme VII

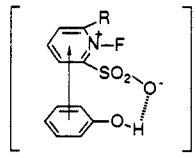


with 2-naphthol in methylene chloride, the system immediately became orange, and this color faded as fluorination proceeded. Scheme VI exemplifies the reaction mechanism with enol ethers. Electron transfer through the formation of π-complex **101**, followed by F• transfer gives the intermediate fluoro carbocation **102**, whose subsequent reactions lead to α-fluoro ketones **55**, **61**, **65**, **67**, etc. provided R is an easily eliminatable Me_3Si or CH_3CO group, or pyridinium fluoro salts **47**, **49**, and **53** should R be an alkyl. The presence of complete carbocations is supported by the finding that *trans*- and *cis*-β-methylstyrene gave the same 1:1 mixtures of erythro and threo fluoro products.

Reactions of the strongest pentachloro salt **6** were somewhat different. Solvent addition products **52**, **92–95**, **97**, and **98** and proton-elimination products **96** and **99** can be explained on the basis of the extremely low nucleophilicity of the resulting pentachloropyridine.

Among the reactions of olefins with **6**, 1,1-dialkylated and 1,1,2-trialkylated ethylenes such as 2-methyl-1-pentene and 4-methyl-1-phenyl-3-pentene afforded fluorinated products, while 1-alkylated and 1,2-dialkylated ethylenes such as 1-octene and 2-octene gave no products though other reactions occurred. The ^{19}F NMR of these reactions showed the formation of large amounts of HF. The one-electron-transfer mechanism shown in Scheme VII would adequately explain this. The great difference between the types of alkylated ethylenes is an indication that the stability or lifetime of the intermediate radical cation species **103** may possibly be a decisive factor in the formation of fluoro products. The radical cation **103** (R^1 = alkyl, $R^2 = R^3 = R^4$ = H or $R^1 = R^4$ = alkyl, $R^2 = R^3$ = H) of the latter type of ethylenes is thus so labile as to decompose before catching F• from **104**, while **103** ($R^1 = R^2$ = alkyl, $R^3 = R^4$ = H or $R^1 = R^2 = R^3$ = alkyl, R^4 = H) of the former ethylenes stabilized by a tertiary carbon have a lifetime sufficiently long enough to catch F•. The decomposition of **104** itself should result in the formation of HF since F• abstracts a hydrogen atom, probably from the solvent. It would also follow that styrene or its derivatives should give the fluorinated

Chart III



π-complex
(R=H, Cl)

products in high yields. The resulting styrene radical cations may be stabilized by the strong effect of a phenyl group.

Selectivity in Fluorination. The exclusive ortho and para fluorinations of phenols and aniline derivatives reflect the actual electrophilic character of *N*-fluoropyridinium salts. In the fluorination of phenol itself, ortho/para orientation was far superior to that of XeF_2 in which the meta isomer was formed in the same yield as the para isomer (*o*:*m*:*p* = 2:2:1)[10a] and differed only slightly with that of $CsSO_4F$ by which the meta isomer was scarcely formed.[11a]

As seen in Table II, the ortho/para fluorination ratio of phenol varied remarkably with the structure of *N*-fluoropyridinium salts. The ortho/para ratios of triflates **1**–**6** were in the range of 1.3–3.3 and that of tetrafluoroborate **3a**, 8.4. Counteranion-bound salts **12** and **13** gave the ortho isomer only. These results demonstrate the crucial function of the counteranion part to be the formation of hydrogen bonding with phenolic hydrogen. Thus, the exclusive ortho fluorination of **12** and **13** can be explained by the conformation of the π-complex fixed by hydrogen bonding between OH and bound SO_3^-, so that the N–F part is situated near ortho positions during the reaction, as shown in Chart III.

The high ortho/para ratio (8.4) of **3a** compared with that (3.3) of triflate **3** is reasonable in consideration of the hydrogen bonding of $^-BF_4$ which should cause the positive N–F part to remain nearby by electrostatic force. The low ratios (1.5–1.3) of **2**, **4**, and **5** compared with those (2.5–3.3) of **1**, **3**, and **6** may be due to the relative bulkiness of the groups in the vicinity of N–F which may hinder its approach to OH.

As suggested by Appleman et al., the reported high ortho/para ratios (10–14) of an ionic reagent $Cs^+{}^-OSO_3F$[11a] can be explained by similar hydrogen bonding between OH and $^-OSO_3F$. This would also be strong support for the possibility that preferential ortho fluorination of phenol with molecular fluorine (F_2) is due to a six-membered transition state involving the hydrogen bonding between the OH and polarized fluorine, $F^{\delta+}\cdots F^{\delta-}$.[34]

In the fluorination of aniline derivatives, almost exclusive ortho fluorination of the counteranion-bound salt **13** can be visualized by consideration of similar hydrogen bonding between the NH and counteranion part. For preferential ortho fluorination with CF_3OF, Fifolt et al. has indicated a mechanism involving hydrogen bonding between NH and the oxygen atom of CF_3OF as one of two possible mechanisms.[35]

Table IV shows the pyridine ring substituent effect on the ortho and ipso fluorination of para-alkylated phenol **27**. While salts **1**, **2**, **3**, **5**, and **6** brought about exclusive ortho fluorination, salts **4**, **7**, and **9** each possessing two bulky α-substituents produced the fluoro dienone **29** from ipso fluorination along with *o*-fluoro isomer **28**. The more bulky salt **4** gave a considerable amount of **29**, while smaller amounts were obtained by less bulky **7** and **9**. The fluorination of OH-protected **24** with **4** gave a higher proportion of **29**. Tyrosine derivative **19** and estrone **21** were exclusively fluorinated at ortho positions with **3**, **2**, or **7**. These ortho/ipso selectivities were compared with those reported for other electrophilic reagents. Both the fluorination of tyrosine **19** with CF_3OF[36] and that of estrone with $FClO_3$[37] underwent the ipso fluorination exclusively, giving the corresponding fluoro dienones. Estrone 3-methyl ether and estrone 3-acetate still gave the fluoro dienone along with small amounts of *o*-fluoro isomers on treatment with CF_3OF.[38] Thus, sterically small and nonionic reagents undergo ipso fluorination, possibly due to the low formation energy of the *p*-quinonoid type of intermediate compared with the corresponding *o*-quinonoid intermediate. However, ionic $CsSO_4F$ reacted with 17β-estradiol to give *o*-fluoro derivatives only.[39] These data again indicate conformation fixation by hydrogen bonding to be crucial for the ortho fluorination of para-alkylated phenols. The favorable ortho fluorination of *p*-cresol with F_2 thus provides additional support for the presence of the six-membered transition state mentioned above.[40]

The reaction of $FClO_3$ with sodium salt of diethyl malonate resulted in the formation of the difluoride according to Inman's report,[41] while 2,4,6-trimethyl salt **2** gave the monofluoride in good yield. Thus it may be difficult for **2** to produce the difluoride, judging from the low yield of the difluoride on treatment with the sodium salt of diethyl monofluoromalonate. That sodium salt of diethyl monochloromalonate was smoothly fluorinated by **2** to give the chlorofluoromalonate in high yield is a significant finding. The difference between the fluoro and chloro substituents appears to be related to the different keto–enol equilibrium of the sodium salts. The results of the Lewis acid-catalyzed fluorination shown in Table VIII lend support to this view. Thus, with the $ZnCl_2$ catalyst and two equivalent amounts of **2**, easily enolizable β-diketone **43** produced difluoride **44**, while hardly enolizable diethyl malonate could give only the monofluoride. The intermediate enolizable β-keto ester gave a mixture of mono- and difluoride (runs 3 and 4, Table VIII). A strong Lewis acid $AlCl_3$ was capable of converting diethyl malonate to the difluoride in good yield.

As indicated by the experiments in eq 7 and runs 5–8 in Table XII, salt **1** can clearly distinguish two reactive moieties such as an enol silyl ether moiety and olefin moiety or an activated aromatic ring, a conjugated vinyl acetate and a nonconjugated vinyl acetate moiety, and an enol silyl ether and a conjugated vinyl acetate moiety. Each of the former moieties was fluorinated exclusively. From a synthetic standpoint, this selectivity is of great use since, otherwise, the other reactive moieties would have to be protected by chemical conversion. The almost exclusive fluorination of trialkylated moiety among di- and trialkylated enol silyl ether moieties as shown in run 9 in Table XII clearly confirmed the superior regioselectivity of the *N*-fluoropyridinium salt system. This new, selective fluorination of the 9α-position of steroids should provide a very useful means for preparing biologically important 9α-fluoro steroids.[42] The one-electron-transfer mechanism through the π-complex discussed above may serve as an explanation for this superiority. The experiments in runs 1–3 and 9 in Table XII show the reactivity of alkylated enol ethers toward **1** to remarkably increase with the number of alkyl groups as exemplified in eq 10. Since the ionization potential of ethylene decreases as the number of alkyl substituents increases,[43] π-complex formation followed by electron transfer should occur easily in the above order.

$$CH_2{=}CR(OSiMe_3) < R'CH{=}CR(OSiMe_3) < R'R''C{=}CR(OSiMe_3)\ (R,R',R'' = \text{alkyl}) \quad (10)$$

Regioselectivity was found to vary according to the structure

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(35) Fifolt, M. J.; Olczak, R. T.; Mundhenke, R. F. *J. Org. Chem.* **1985**, *50*, 4576.
(36) Barton, D. H. R.; Hesse, R. H.; Pechet, M. M.; Toh, H. T. *J. Chem. Soc., Perkin Trans 1* **1974**, 732.
(37) Mills, J. S.; Barrera, J.; Olivares, E.; Garcia, H. *J. Am. Chem. Soc.* **1960**, *82*, 5882.
(38) (a) Airey, J.; Barton, D. H. R.; Ganguly, A. K.; Hesse, R. H.; Pechet, M. M. *Anales Quimica* **1974**, *70*, 871. (b) Chavis, C.; Mousseron-Canet, M. *Bull. Soc. Chim. Fr.* **1971**, 632.
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(43) (a) Robinson, J. W. *Handbook of Spectroscopy*; CRC Press: 1974; Vol. 1, pp 257–511. (b) Kimura, K.; Katsumata, S.; Achiba, Y.; Yamazaki, T.; Iwata, S. *Handbook of Hel Photoelectron Spectra of Fundamental Organic Molecule*; Japan Scientific Societies Press/Halsted Press: 1981.

of *N*-fluoropyridinium salts. Thus, contrary to unsubstituted salt **1**, 2,4,6-trimethyl salt **2** failed to produce any 9α-fluoro steroid **74** from **73**. The bulkiness of **2** appears quite likely the reason for this. Thus, **2** was unable to approach the crowded 9-position.

Stereoselectivity also remarkably varied according to the structure of *N*-fluoropyridinium salts. As shown in Table X, **1** reacted with steroid **57** to give a 1:2 mixture of 6α- and 6β-isomeric steroids, and bulky **2** or **7** almost exclusively gave the 6β-isomer, possibly as a result of the fluorination at the less hindered β-side. Stereoselective fluorination regulated by structural variation should thus find useful application.

The fluorination yields of enamines **59a-c** showed considerable variation according to the electronic nature of the amine part. The pK_a values of enamines of isobutyraldehyde have been shown to increase in the order of morpholino (pK_a 5.47), piperidino (8.35), and pyrrolidino (8.84).[44] Steroid enamines should show essentially the same order. Consistent with this, the least basic morpholino steroid **59a** afforded the best yield of fluorinated product **75**, while the most basic pyrrolidino **59c** gave the lowest yield and large amounts of unidentified products. The milder *N*-fluoropyridinium salt **2** gave better yields.

A comparison was made of the regioselectivity in the 4- and 6-fluorinations of steroids with salt **1** among enamines **59**, vinyl ester **57**, enol alkyl ether **56**, and enol silyl ether **58**. The most electron-deficient **57** produced 6-fluoro steroids exclusively, while the most electron-rich **59** gave only the 4-fluoro steroid. Intermediate electron-rich **58** and **56** yielded ca. 1:2 and 1:1 mixtures of 4- and 6-isomers, respectively. Similar regioselectivity has been found in fluorination with CF_3OF[45] or $FClO_3$.[46] Differences in electron distribution in the conjugated diene moiety of the substrates themselves rather than the nature of *N*-fluoropyridinium salt **1** may thus be the reason for this regioselectivity.

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Conclusions

N-Fluoropyridinium salts provide a new system of fluorinating agents by which a wide range of nucleophilic substrates differing in reactivity can be fluorinated due to the varying degree of fluorinating power and also fluorinated very selectively through structural alteration. The scope of selective fluorination should be broadened considerably on the basis of the present results. The *N*-fluoropyridinium salt system should thus make possible the preparation of many useful organofluoro compounds.

Acknowledgment. The authors express their appreciation to Tsuyoshi Aoki (from Toaeiyo Co., Ltd.) for preparing fluoro lactones **88**, **90**, and **91**.

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Communications to the Editor

New Synthetic Route to Unsymmetrically Substituted Pentacoordinated Phosphorus. Hydrolytically Stable Chiral Monocyclic Oxyphosphoranes

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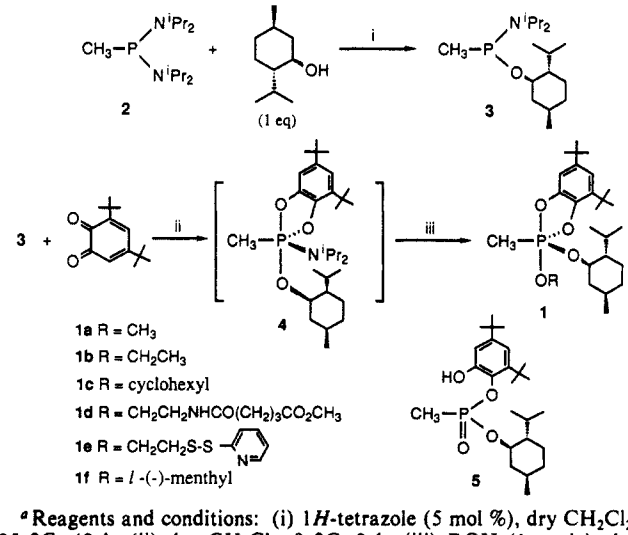
Pentacoordinated phosphorus (phosphoranes) are of interest as models for the intermediate or transition state for phosphoryl transfer occurring in the hydrolysis of phosphates and phosphonates.[1a-d] Such intermediates have been proposed for an increasing number of reactions catalyzed by phosphoryl- and nucleotidyl-transfer enzymes.[1c,2] Monocyclic oxyphosphoranes represent an important stable model system for such intermediates. The stereochemical course of phosphoryl-transfer reactions has been discussed in terms of structure, stereochemistry, and pseudorotational processes observed for model phosphoranes.[1b] However, the monocyclic phosphoranes synthesized to date are invariably "symmetric" phosphoranes in the sense that at least two or three identical alkoxy substituents are bound to phosphorus. The proposed intermediates or transition states in phosphoryl-transfer reactions frequently involve "unsymmetric" oxyphosphoranes possessing five different substituents bound to phosphorus. No general synthetic method for such unsymmetric phosphoranes has been reported.

We now describe a novel synthetic route to the unsymmetric methylphosphoranes **1a-e** having one *l*-menthoxy group and various other alkoxy groups bound to phosphorus. The key synthetic step in this process is the direct displacement of the *N,N*-diisopropylamino group in the intermediate **4** by alcohols (Scheme I). Methylphosphoranes **1a-e** were obtained in high yield after purification via column chromatography under basic conditions (Table I).

Scheme I[a]



[a] Reagents and conditions: (i) 1*H*-tetrazole (5 mol %), dry CH_2Cl_2, 25 °C, 40 h; (ii) dry CH_2Cl_2, 0 °C, 2 h; (iii) ROH (1 equiv), dry CH_2Cl_2, 25 °C, overnight.

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