Synthesis, Properties, and Reactivity of *N,N′*-Difluorobipyridinium and Related Salts and Their Applications as Reactive and Easy-To-Handle Electrophilic Fluorinating Agents with High Effective Fluorine Content[1]

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N,N′-Difluoro-2,2′-, -2,4′-, -3,3′-, -4,4′-bipyridinium and substituted *N,N′*-difluoro-2,2′-bipyridinium bis(triflates), bis(tetrafluoroborates), bis(hexafluorophosphates), and bis(hexafluoroantimonates) **1**−**9** were synthesized in high yields by the direct fluorination of a mixture of a bipyridyl and a Lewis acid, a Brønsted acid, or the alkali metal salt of an acid. The higher homologues, trimer **10** and polymer **11**, were also synthesized. Unsubstituted or electron-donating group-substituted *N,N′*-difluorobipyridinium salts are stable nonhygroscopic crystals, while the electron-withdrawing group-substituted *N,N′*-diflurobipyridinium salts **3**, **5**, and **6** are moisture-sensitive crystals. Hydrolysis of **1b** in boiling water gave 3,3′-dihydroxy-2,2′-bipyridyl. The reactivity determination indicated that the fluorinating capability decreased in the order 2,2′- ≫ 2,4′ > 3,3′- ≈ 4,4′-isomer ≫ *N*-fluoropyridinium salt and that the two N−F moieties in a molecule were effective for fluorination. This fluorination occurred in a step-by-step manner, and the reactivity difference between the first and second fluorinations was very small. *N,N′*-Difluoro-2,2′-bipyridinium bis(tetrafluoroborate) (**1b**) is thus shown to be a highly reactive and easy-to-handle electrophilic fluorinating agent with the high effective fluorine content (103.3 g/kg) for preparing many fluoro organic compounds.

Introduction

Electrophilic fluorinating agents are required for preparing fluoro organic compounds in advanced organic synthesis at present,[2] and many compounds with an N−F moiety have thus been made available as electrophilic fluorinating agents.[2,3] These compounds include *N*-fluorosulfonamides,[4] *N*-fluoropyridinium salts,[5] *N*-fluoropyridinium-2-sulfonates,[6] *N*-fluorobis(trifluoromethanesulfonyl)imides,[7] *N*-fluorosultums,[8] *N*-fluorodisulfonimides,[9] *N*-alkyl-*N′*-fluoro-1,4-diazoniabicyclo[2.2.2]octane salts,[10] *N*-fluoro-*N′*-hydroxy-1,4-diazoniabicyclo[2.2.2]-octane salts,[11] *N,N′*-difluoro-1,4-diazoniabicyclo[2.2.2]-octane salts,[12] and *N*-fluoro oxathiazine dioxides.[13] Some of these reagents appear on the market.[14] But due to the low effective fluorine content (54−78 g/kg[15]), reactive reagents possessing more effective fluorine content are desired. The authors have recently produced highly reactive and easy-to-handle *N,N′*-difluoro-1,4-diazoniabicyclo[2.2.2]octane salts each containing two N−F moieties in a molecule.[12] One N−F moiety is effective for fluorination, and the other promotes the fluorination reactivity. Thus, its effective fluorine content is 59 g/kg at most. *N*-Fluoropyridinium tetrafluoroborate previously synthesized by the authors[5b−d] is not particularly reactive but has a high effective fluorine content (102.7 g/kg). The studies on *N*-fluoropyridinium salts by the authors have also shown that the fluorination

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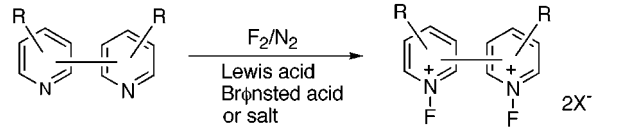
Scheme 1



No.	bonding	R	X
1	2,2′	H	**a** OTf
2	2,2′	4,4′-diCH_3	**b** BF_4
3	2,2′	4,4′-diCl	**c** PF_6
4	2,2′	4,4′-diC_6H_5	**d** SbF_6
5	2,2′	4,4′-diCO_2CH_3	
6	2,2′	5,5′-diCF_3	
7	2,4′	H	
8	3,3′	H	
9	4,4′	H	

reactivity varies with the electron density of the N−F site, and electron-withdrawing group-substitution of *N*-fluoropyridiniums enhances the reactivity.[5b−d,6] Its dimeric *N,N*′-difluorobipyridinium salt was thus made into a desired fluorinating agent, because each of two *N*-fluoropyridinium moieties could act not only as a fluorine source but also as an electron-withdrawing substituent. Recently, Banks et al. reported the synthesis of *N,N*′-difluoro-4,4′-bipyridinium bis(triflate), *N*-fluoro-*N*′-methyl-4,4′-bipyridinium bis(triflate), and *N*-fluoro-4-(4′-pyridyl)pyridinium tetrafluoroborate−BF_3 complex.[16] This paper presents the synthesis, properties, and reactivity of a series of *N,N*′-difluorobipyridinium and related salts, and the 2,2′-isomeric salt is assessed for its usefulness as an electrophilic fluorinating agent.

Results and Discussion

Synthesis of *N,N*′-Difluorobipyridinium and Related Salts. Isomeric *N,N*′-difluorobipyridinium salts and derivatives **1**−**9** (Scheme 1) and higher homologues **10** and **11** (Figure 1) were synthesized by the direct fluorination of a mixture of a bipyridyl or its homologue and a Lewis acid, a Brønsted acid, or the alkali metal

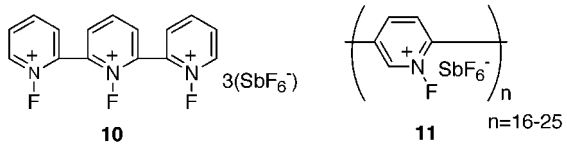


Figure 1.

salt of an acid in acetonitrile or in a mixture of acetonitrile and formic acid at −40 to 0 °C with 10−20% F_2/90−80% N_2. The reaction conditions and results are specified in Table 1. Fluorination yields were affected by the solubility of the complexes and salts of the bipyridyls with the Lewis and Brønsted acids. To enhance fluorination yields of poorly soluble complexes and salts, a 49:1 or 50:1 (v/v) mixture of acetonitrile and formic acid or excess acetonitrile as the solvent, fluorine in large excess, and slightly less acid (1.84−1.97 molar equiv) were used.

Conjugated *N,N*′-difluoro-2,2′-, -2,4′- and -4,4′-bipyridinium bis(triflates), **1a**, **7a**, and **9a**, were synthesized in high yields by the fluorination of a 1:2 molar mixture of bipyridyl and triflic acid (runs 1, 2 and 4); this mixture is a dihydrogen salt of the bipyridyl with triflic acid. It was not possible by this method to produce a nonconjugated 3,3′-isomer **8a**, and the starting dihydrogen salt of 3,3′-bipyridyl with triflic acid remained unreacted. This outstanding difference between conjugated and nonconjugated isomers cannot be explained at present, but possibly it may be due to interactions of π-electrons of one ring of the dihydrogen bipyridinium salts with F_2, which may activate the NH site of the other ring in the conjugated system. Triflate **8a** was thus synthesized by the fluorination of free 3,3′-bipyridyl in the presence of lithium triflate (run 3).

2,2′-Bis(tetrafluoroborate) **1b** was synthesized by the fluorination of a 1:2 molar mixture of bipyridyl and BF_3 in acetonitrile at −20 °C and more efficiently in a 50:1 (v/v) mixture of acetonitrile and formic acid at 0 °C. The latter method is particularly advantageous, since the final product **1b** is obtained as pure crystals from the starting homogeneous reaction solution with the course of fluorination and pure **1b** is easily produced in high yield by filtering the reaction mixture after fluorination. This method was successfully conducted on a large scale using 4 mol of 2,2′-bipyridyl.[17]

N,N′-Difluoro-2,4′-bipyridinium bis(tetrafluoroborate) (**7b**) and *N,N*′-difluoro-4,4′-bipyridinium bis(tetrafluoroborate) (**9b**) were obtained by the fluorination of a 1:1.95−1.96 molar mixture of bipyridyl and BF_3 (runs 8 and 9), since the 1:2 complex of 2,4′-bipyridyl or 4,4′-

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(15) Effective fluorine contents: 54 g/kg for Selectfluor,[14] 59 g/kg for NFTh,[14] 75 g/kg for Onoda Fluorinate FP-B800 (*N*-fluoro-2,6-dichloropyridinium tetrafluoroborate).[14]

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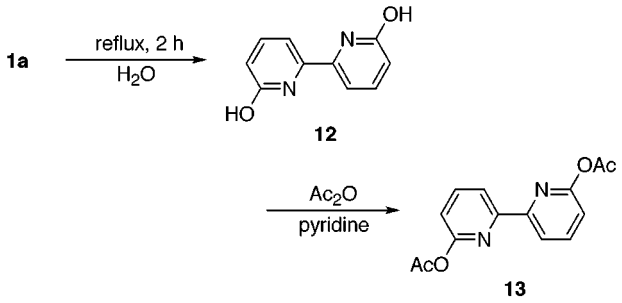
(17) A large scale synthesis of *N,N*′-difluoro-2,2′-bipyridinium bis(tetrafluoroborate) (**1b**) was carried out as follows: 2,2′-bipyridyl (4 mol, 625 g), CH_3CN (10.0 L), and formic acid (0.2 L) were placed in the reactor of a fluorination apparatus.[5c,e] Commercially available CH_3CN and formic acid as the solvents were used without further purification or dryness. A separable flat-bottom type of cylindrical stainless reactor (20 L, 30 cm ∅) was used, the inside of which is coated with a fluoro resin. To the solution was added a BF_3/CH_3CN solution (16.0 wt%, 3.9 L), and then the charged reactor was purged with N_2 and placed on an ice bath at 0 °C. A 20% F_2−80% N_2 (v/v) gas mixture was then introduced at a flow rate of 4.5 to 3.0 L min^{-1} just above the surface of the rapidly stirred (950 rpm) reaction mixture. A cornical nozzle was used so that the fluorination proceeded rapidly; the nozzle made the F_2/N_2 gas contact the surface of the solution very effectively. After the flow of F_2 (8.6 mol) was stopped, only N_2 was passed through the flask at a rate of 80 mL min^{-1} for 30 min. The resulting precipitate was collected by filtration under dry atmosphere and was washed with CH_3CN (1 L × 2) to give 1278 g (87%) of pure **1b**. The crystals were dried at 50 °C for 5 h under reduced pressure.

Table 1. Synthesis of *N,N′*-Difluorobipyridinium Salts and Related Salts

run	bipyridyl	mmol	solvent (mL)	acid or salt	bipyridyl/acid or salt/F_2 (molar ratio)	temp (°C)[a]	product	yield (%)[b]
1	2,2′-	5	CH_3CN(20)	TfOH	1/2/2.3	−20	**1a**	86
2	2,4′-	5	CH_3CN(20)	TfOH	1/2/2.3	−20	**7a**	92
3	3,3′-	5	CH_3CN(10)	TfOLi	1/2/3	−40	**8a**	75
4	4,4′-	5	CH_3CN(20)	TfOH	1/2/2.3	−20	**9a**	91
5	2,2′-	5	CH_3CN(20)	BF_3	1/2/3	−20	**1b**	87
6	2,2′-	25	CH_3CN/HCOOH[d] (76.5) 50/1 v/v	BF_3	1/2/2.2	0	**1b**	89
7	2,2′-	6	CH_3CN(100)	HBF_4	1/2/5.4	−20	**1b**	90
8	2,4′-	10.3	CH_3CN(40)	BF_3	1/1.96/4.4	−20	**7b**	86
9	4,4′-	4.26	CH_3CN/HCOOH[d] (8.57) 49/1 v/v	BF_3	1/1.95/6.1	0	**9b**	95
10[c]	2,4′-	2.1	CH_3CN(30)	HPF_6	1/1.91/4.4	−20	**7c**	64
11	4,4′-	9.18	CH_3CN(40)	SbF_5	1/1.95/4.4	−20	**9d**	91
12	4,4′-diCH_3-2,2′-	6	CH_3CN(24)	BF_3	1/1.9/4.6	−20	**2b**	73
13	4,4′-diCl-2,2′-	1.09	CH_3CN(2.2)	BF_3	1/2.01/4.4	−20	**3b**	79
14	4,4′-diC_6H_5-2,2′-	3.2	CH_3CN(12)	BF_3	1/1.84/4.2	−20	**4b**	64
15	4,4′-diCO_2CH_3-2,2′-	0.88	CH_3CN(1.8)	SbF_5	1/2.0/4.4	−20	**5d**	97
16	5,5′-diCF_3-2,2′	3	CH_3CN(15)	TfOH	1/1.97/4.4	−20	**6a**	72
17	terpyridine	2.36	CH_3CN(30)	SbF_5	1/2.95/6.7	−20	**10**	quant[e]
18	polypyridine	4.47	CH_3CN(50)	SbF_5	1/1/3.7	−20	**11**	quant[e]

[a] Bath temperature. [b] Isolated yield. [c] In this experiment, a mixture of 2.0 mmol of *N,N′*-dihydro-2,4′-bipyridinium bis(hexafluorophosphate) and 0.1 mmol of 2,4′-bipyridyl was used as the starting material. The bis(hexafluorophosphate) was prepared from 2,4′-bipyridyl and HPF_6 in a separate experiment (see Materials of Experimental Section). [d] Commercially available formic acid was used without further purification. [e] Quantitative yield.

Scheme 2



bipyridyl and BF_3 was noted to very poorly soluble in acetonitrile. Bis(hexafluorophosphate) and bis(hexafluoroantimonate) **7c** and **9d** were synthesized using HPF_6 and SbF_5, respectively (runs 10 and 11).

The higher homologues, *N,N′,N″*-trifluoro-terpyridinium salt **10** and poly(*N*-fluoropyridinium salt) **11**, were produced quantitatively by the fluorination of terpyridine and polypyridine,[18] respectively, using SbF_5 in acetonitrile.

Properties of *N,N′*-Difluorobipyridinium Salts. *N,N′*-Difluorobipyridinium salts substituted or unsubstituted with electron-donating groups are stable nonhygroscopic crystalline solids. The salts substituted with electron-withdrawing groups, **3**, **5**, and **6**, are moisture-sensitive solids. Thus, it was not possible to obtain dichloro, bis(trifluoromethyl), and bis($COOCH_3$) derivatives **3b**, **5d**, and **6a**, as pure crystals for elemental analysis. Tetrafluoroborate **1b** was hydrolyzed in boiling water for 2 h to give 3,3′-dihydroxy derivative **12**, which was isolated in 80% yield as diacetate **13** by treatment with acetic anhydride (Scheme 2). The alkaline hydrolysis of **1b** occurred readily at room temperature and was complete at 1 h. Dihydroxy **12** was isolated as diacetate **13** in 23% yield from the reaction mixture, and other products were not characterized. Hydrolysis product **12** formation should occur via the carbene mechanism previously proposed for the novel base-initiated decomposition of *N*-fluoropyridinium salts.[5f,19]

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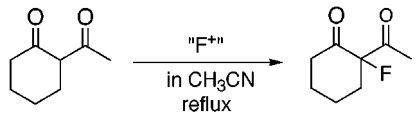
Table 2. Controlled Fluorination of 2-Acetylcyclohexanone (15)[a]



15 (1 mmol) **16**

run	"F^+" (mmol)	reaction time[b]	yield (%) of **16**[c]
1	2,2′-isomer **1a** (0.5)	<5 min	85
2	2,4′-isomer **7a**(0.5)	2 h	78
3	3,3′-isomer **8a** (0.5)	5 h	70
4	4,4′-isomer **9a** (0.5)	5 h	87
5	*N*-fluoropyridinium triflate (**14**) (1)	19 h	79

[a] **15** (1 mmol) was allowed to react with "F^+" (0.5 or 1 mmol) in acetonitrile under reflux, and the reaction was traced by checking with a paper absorbing aqueous KI solution. [b] Each reaction time was the time when "F^+" was consumed, except for run 5 where "F^+" was not completely consumed. [c] Yields were determined by ^{19}F NMR and calculated on the basis of **15**.

Fluorination Reactivity of Isomeric *N,N′*-Difluorobipyridinium Salts. Relative reactivity was determined as 2,2′- (**1a**) ≫ 2,4′- (**7a**) > 3,3′- (**8a**) ≈ 4,4′-isomer (**9a**) ≫ *N*-fluoropyridinium triflate (**14**) by the controlled reaction of 0.5 mmol of triflate (**1a**, **7a**, **8a**, or **9a**) or 1 mmol of **14** with 1 mmol of 2-acetylcyclohexanone (**15**) to give fluoro product **16** shown in Table 2 and Figure 2. Table 2 shows the reaction time required for consuming *N,N′*-difluorobipyridinum triflate at reflux temperature, and Figure 2 shows the formation curves (vs time) of **16** by reactions at 50 °C. The lowest reactivity noted for the 4,4′-isomer as a bipyridinium salt indicates the π-electron conjugation effect to be unessential for fluorination, since the 4,4′-dipyridinium salt may exert strong π-electron conjugation effect.[20] This would explain why 2,2′-isomer **1a** reacted more rapidly (<5 min) than any

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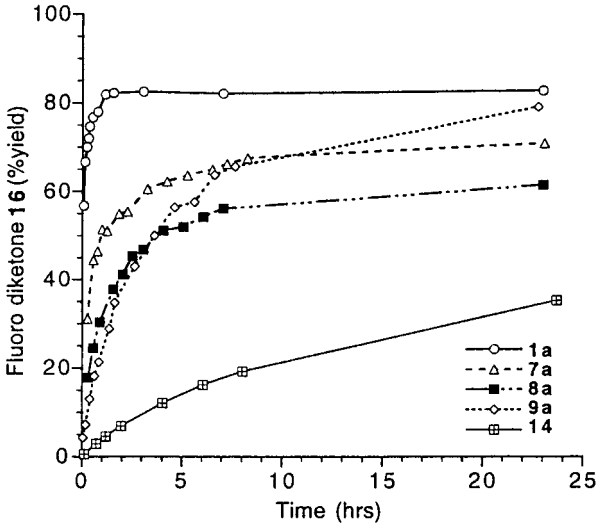
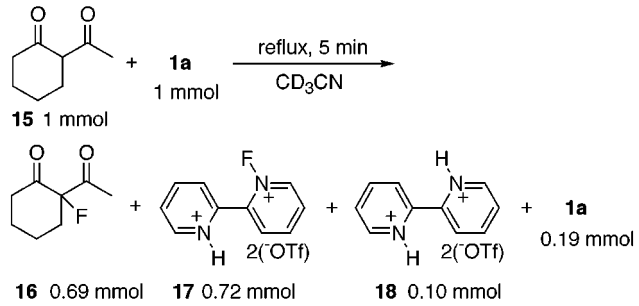


Figure 2. Formation curves of fluoro diketone **16** by the fluorination of diketone **15** with **1a**, **7a**, **8a**, **9a**, or **14** in CD_3CN at 50 °C. The formation of **16** was monitored by ^{19}F NMR (see Experimental Section).

Scheme 3



other isomer to give 85% of **16**, while 3,3′- and 4,4′-isomers **8a** and **9a** reacted the most slowly (5 h). The single pyridinium ring salt **14** also reacted slowly (19 h). Fluorinating capacity was previously shown to be correlated to the acidity (pK_a) of nitrogen lone pairs of the original pyridines.[5d] The relative reactivity order is thus consistent with pK_a of bipyridyls, as follows; 2,2′-bipyridyl ($pK_{a1} = -0.2$) ≫ 4,4′-bipyridyl ($pK_{a1} = 2.69$) ≫ pyridine ($pK_a = 5.42$).[21] The highest reactivity of the 2,2′-isomer would thus be due to the N−F moieties being the most deficient in electrons, and the high capacity of the *N*,*N*′-difluorobipyridinium salt system compared to that of the *N*-fluoropyridinium salt system (**14**) should derive from the strong electron-withdrawing effect of other *N*-fluoropyridinium moieties.

The two N−F moieties of all *N*,*N*′-difluorobipyridinium salt isomers were found to be effective for fluorination; the yields in runs 1−4 in Table 2 exceeded 50%, using a half equimolar amount of an *N*,*N*′-difluorobipyridinium salt.

As shown in Scheme 3, when **15** (1 mmol) reacted with **1a** (1 mmol) for a short time (5 min), the reaction mixture consisted of fluoro product **16** (0.69 mmol, 69%), mono N−F intermediate **17** (0.72 mmol, 72%), **18** (0.10 mmol, 10%), and **1a** (0.19 mmol, 19%), according to ^{19}F and ^{1}H NMR analysis. The structure of intermediate **17** was assigned on the basis of the characteristic N−F moiety fluorine chemical shift at 39.6 ppm. Fluorination by the two N−F moieties thus clearly occurs in a step-by-step manner through **17**, and the reactivity difference between the first and second fluorinations was very small, since final **18** formed even in the presence of starting **1a**. Thus, **17** still retains adequate fluorinating capacity because the resulting *N*-hydropyridinium moiety exerted a fairly strong electron-withdrawing effect. This is also indicated by the formation curve of **16** using **1a** shown in Figure 2, which may be regarded as being due to a single reaction.

The step-by-step reaction of the *N*,*N*′-difluorobipyridinium salt system is in sharp contrast to the *N*,*N*′-difluoro-1,4-diazoniabicyclo[2.2.2]octane salt system in which one N−F moiety functions as a fluorinating agent and the other activates the fluorination; once fluorination occurs by the former, the other N−F moiety immediately decomposes through intramolecular one-electron transfer.[12a]

Fluorination of Nucleophiles by *N*,*N*′-Difluoro-2,2′-bipyridinium Bis(tetrafluoroborate) (1b). Assessment was made of the reactivity of 2,2′-isomeric tetrafluoroborate **1b** toward various nucleophiles, since **1b** is cheap and can be easily prepared. Table 3 shows **1b** to be widely useful as an electrophilic fluorinating agent of diketones, keto esters, ketones, activated aromatics, styrenes, vinyl esters, enol trialkylsilyl ethers, and others in fair to high yields.

The reaction of tetrafluoroborate **1b** with **15** was slow (3 h, reflux) due to low solubility (run 1 in Table 3) compared to that of triflate **1a** (run 1 in Table 2). That of **1b** was greatly accelerated following the addition of a catalytic amount of sodium triflate and was complete at only 10 min to give 82% of **16** (run 2 in Table 3). An explanation for this would be the phase transfer of *N*,*N*′-difluorobipyridinium cations by sodium triflate from a solid to a liquid phase, since triflate **1a** is soluble in the solution. γ-Butyrolactone and formic acid dissolved **1b**, which thus rapidly reacted with **15** in these solvents; the reaction at 80 °C for 5 min in γ-butyrolactone and at reflux temperature for <5 min in formic acid gave 77 and 75% of **16**, respectively.

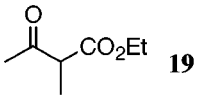
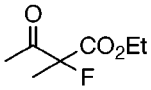
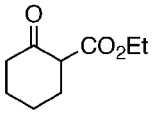
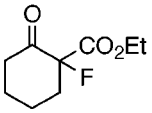
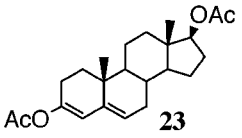
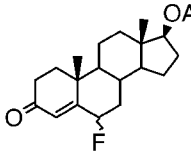
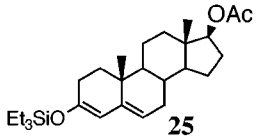
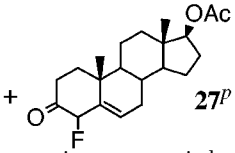
N-Chloromethyl-*N*′-fluoro-1,4-diazoniabicyclo[2.2.2]-octane bis(tetrafluoroborate) (F-TEDA-BF_4) (1 mmol), available commercially, reacted with **15** (1 mmol) under the similar conditions (1.5 h, reflux in 2 mL of acetonitrile) to give **16** in 83% yield. From this, the reactivity of **1b** is of the same order as that of F-TEDA-BF_4.

The difluorination of dibenzoylmethane in acetonitrile was accelerated by a catalytic amount of triflic acid (run 3). The reaction in formic acid (65 °C, 3 h) without triflic acid gave a 1:1 mixture of mono- and difluorides in 88% yield. **1b** failed to react with diethyl malonate. Activated aromatics were smoothly fluorinated by **1b** (runs 6−11) and even more so with a catalytic amount of sodium triflate (run 7). Resorcinol was fluorinated at the 4- or 6-position in good yield. Methylstyrene was smoothly fluorinated with **1b** (run 12), while styrene fluorination was difficult. Fluorination of 2-tetralone gave 1-fluoro-2-tetralone (run 13), and that of 1-tetralone gave a 6.3:1 mixture of 2-fluoro- and 2,2-difluoro-1-tetralone in 44% yield (reflux, 16 h).

The vinyl acetate of steroid **23** was fluorinated by **1b** to give 6-fluoride **24** in high yield (run 14) when done in the presence of sodium bicarbonate as an acid trap, without which, the yield of **24** was decreased, since **24**

(21) *Kagaku Binran, Kiso-hen;* 4th ed.; Chemical Society Japan; Maruzen Ltd.: Tokyo, 1993; p 320.

Table 3. Fluorination of Various Nucleophiles with *N,N′*-Difluoro-2,2′-bipyridinium Bis(tetrafluoroborate) (1b)

run[a]	nucleophile	additive (mmol)	solvent	conditions	product	yield(%)[b]
1	2-Acetylcyclohexanone(**15**)	none	CH_3CN	reflux,3h	2-Acetyl-2-fluoro-cyclohexanone(**16**[c])	71
2	**15**	NaOTf (0.1)	CH_3CN	reflux,10min	**16**[c]	82
3	Dibenzoylmethane	TfOH (0.1)	CH_3CN	reflux,48h	Dibenzoylfluoromethane[d] Dibenzoyldifluoromethane[d]	10 76
4	 **19**	none	CH_3CN	reflux,8h	 **20**[e]	73
5	 **21**	none	CH_3CN	reflux,8h	 **22**[f]	76
6	Phenol	none	CH_3CN	reflux,8h	*o*-Fluorophenol *p*-Fluorophenol 2,4-Difluorophenol	39[g] 33[g] 5[g]
7	Phenol	NaOTf (0.1)	CH_3CN	reflux,5h	*o*-Fluorophenol *p*-Fluorophenol 2,4-Difluorophenol	43[g] 31[g] 6[g]
8	Anisole	none	CH_3CN	reflux,9h	*o*-Fluoroanisole *p*-Fluoroanisole 2,4-Difluoroanisole	40[g] 28[g] 8[g]
9	Phenylurethane	none	CH_3CN	reflux,48h	*o*-Fluorophenylurethane *p*-Fluorophenylurethane 2,4-Difluorophenylurethane	48[g] 32[g] 5[g]
10	Resorcinol	none	CH_3CN	reflux,<5min	4-Fluororesorcinol[h] 4,6-Difluororesorcinol 2-Fluororesorcinol[h]	72[g] 10[g,i] 3[g,i]
11	2-Naphthol	none	HCOOH	rt,10min	1-Fluoro-2-naphthol[j] 1,1-Difluoro-2-naphthalenone[j]	61 18
12	*trans*-PhCH=CHCH$_3$	none	AcOH	reflux,15min	PhCH(OAc)CHFCH$_3$[k]	51
13	2-Tetralone	none	CH_3CN	reflux,10min	1-Fluoro-2-tetralone[l]	38
14	 **23**	$NaHCO_3$ (0.25)	CH_3CN	70°C,1h	 **24**[m,n]	82
15	 **25**	$NaHCO_3$ (0.25)	CH_3CN	rt,30min	**24**[o] +  **27**[p]	65 (**24**/**27**=46/19)

[a] In all runs, each reaction mixture was stirred under N_2. For runs 1, 2, and 4−13, the reaction was carried out in 2 mL of a solvent using 1.0 mmol of a nucleophile and 0.5 mmol of **1b**; for run 3, the reaction was carried out in 2 mL of a solvent using 0.5 mmol of a nucleophile and 0.5 mmol of **1b**; for run 14, the reaction was carried out in 1 mL of a solvent using 0.5 mmol of a nucleophile and 0.25 mmol of **1b**; for run 15, the reaction was carried out in 2 mL of CH_3CN using 0.5 mmol of a nucleophile and 0.25 mmol of **1b**. [b] Determined by ^{19}F NMR using fluorobenzene as an internal standard, based on the amount of a nucleophile used, unless otherwise noted. [c] Lerman, O.; Rozen, S. *J. Org. Chem.* **1983**, *48*, 724. [d] Reference 5d. [e] Kitazume, T.; Kobayashi, T. *J. Fluorine Chem.* **1986**, *31*, 357. [f] Chambers, R. D.; Greenhall, M. P.; Hutchinson, J. *Tetrahedron* **1996**, *52*, 1. [g] The yields were calculated on the basis of the nucleophiles consumed. The conversions of the nucleophiles were 82, 80, 85, 88, and 79% for runs 6, 7, 8, 9, and 10, respectively. [h] Patrick, T. B.; Darling, D. L. *J. Org. Chem.* **1986**, *51*, 3242. [i] The separation of 4,6-difluororesorcinol and 2-fluororesorcinol by column chromatography on SiO_2 was unsuccessful. [j] Staver, S.; Zupan, M. *J. Org. Chem.* **1985**, *50*, 3609. [k] The ratio of diastereoisomers was 1/1. [l] Reference 11e. [m] Hesse, R. H. *Isr. J. Chem.* **1978**, *17*, 60. [n] A 1:1.7 mixture of 6α- and 6β-fluoro steroids. [o] A 1:1.4 mixture of 6α- and 6β-fluoro steroids. [p] Reference 6.

underwent dehydrofluorination due to the resultant acidic conditions. The enol triethylsilyl ether **25** was fluorinated in good yield under similar conditions (run 15).

Conclusion

Dimeric *N,N′*-difluorobipyridinium and the related salts were synthesized in high yields and, compared to

the monomeric *N*-fluoropyridinium salt, were found to have a high fluorinating capacity due to the electron-withdrawing effect of the N−F moieties. The 2,2′-isomer was found to be the most potent fluorinating agent, of which both N−F moieties were effective for fluorination. *N,N*′-Difluoro-2,2′-bipyridinium bis(tetrafluoroborate) (**1b**) is thus shown to be the fluorinating agent most useful for producing fluoro compounds, because of the high effective fluorine content, the ease of handling, wide application, and the simple one-batch process from 2,2′-bipyridyl which has been produced commercially on a large scale.

Experimental Section

General. ^{1}H and ^{19}F NMR spectra were recorded at 200 or 500 MHz and 188 or 470 MHz, respectively. The solvents for ^{19}F NMR were same as those for ^{1}H NMR, unless otherwise noted. The ^{19}F chemical shifts were given in ppm downfield from $CFCl_3$ as an internal standard. IR spectra of the Nujol method were measured using NaCl plates. The previously reported apparatus was used for the fluorination.[5c,e] A poly(tetrafluoroethylene) flask was used for the experiments in which 60% aqueous HPF_6 was used. The melting and decomposition points were uncorrected.

Materials. A vinyl acetate of steroid and an enol triethylsilyl ether for runs 14 and 15 in Table 3 were prepared according to the literature.[22] The dihydrogen salt, *N,N*′-dihydro-2,4′-bipyridinium bis(hexafluorophosphate), which was used in run 10 of Table 1, was prepared by mixing 2,4′-dipyridyl with 2 molar equiv of 60% aqueous HPF_6 in acetonitrile; the crystals were obtained by complete evaporation of the acetonitrile solvent. 3,3′-Bipyridyl[23] and polypyridine[18] were prepared according to the literature. *N*-Fluoropyridinium triflate and a BF_3/CH_3CN solution (16 wt %) were purchased from Chichibu Onoda Corp. (Japan) and Stella Chemifa Corp. (Japan), respectively. The solvents used for reactions were dried by the usual methods before use, and other commercially available materials were used without further purification, unless otherwise noted.

Synthesis of *N,N*′-Difluoro-bipyridinium Salts. General Procedure. In each experiment, the amounts of a bipyridyl, an acid or a metal salt, and a solvent shown in Table 1 were placed in a flask of the fluorination apparatus. The charged flask was purged with N_2 and placed on a cooling bath at the temperature shown in Table 1. A 10% F_2−90% N_2 (v/v) or a 20% F_2−80% N_2 (v/v) gas mixture was then introduced just above the surface of the rapidly stirred reaction mixture at a flow rate of 5−10 mL min^{-1} per 1 mmol of bipyridyl. The amounts of F_2 used are given in Table 1. After the flow of F_2 was stopped, only N_2 was passed through the flask at a rate of 20 mL min^{-1} for 10 min. For run 10, a mixture of 2.0 mmol of *N,N*′-dihydro-2,4′-bipyridinium bis(hexafluorophosphate) and 0.1 mmol of 2,4′-bipyridyl was used as the starting material, and the bis(hexafluorophosphate) was prepared and isolated as crystals in a separate experiment (see Materials). The posttreatment for runs 1, 2, 4, and 11 were as follows: each reaction mixture was evaporated to dryness under reduced pressure, and the residue was washed with EtOAc to give pure **1a**, **7a**, **9a**, or **9d**. For run 3, the reaction mixture was filtered through Celite to remove the LiF formed, the filtrate was evaporated to dryness under reduced pressure, and the residue was washed with EtOAc to give pure **8a**. For runs 5−7 and 9, the resulting precipitate was collected by filtration and washed with CH_3CN and EtOAc to give pure **1b** and **9b**, respectively. For run 8, the resulting precipitate was collected by filtration to give pure **7b** (71%). In addition, the filtrate was evaporated to dryness under reduced pressure, and the residue was recrystallized from CH_3CN/EtOAc to give additional pure **7b** (15%). For run 10, the reaction mixture was filtered, its filtrate was evaporated to dryness under reduced pressure, and the residue was washed with EtOAc to give pure **7c**. For run 12, the reaction mixture was evaporated to dryness under reduced pressure, and the resulting oil was washed with MeOH/Et_2O and recrystallized from CH_3CN/Et_2O to give pure **2b**. For runs 13, 14, and 16, to the reaction mixture were added 3, 6, and 10 mL of Et_2O, and the resulting precipitate was collected by filtration and washed with Et_2O in a drybox to give **3b**, **4b**, and **6a**, respectively. For run 15, the reaction mixture was evaporated to dryness under reduced pressure, and the residue was washed with Et_2O in a drybox to give **5d**. For runs 17 and 18, the reaction mixture was evaporated to dryness under reduced pressure, and the residue was washed with Et_2O to give pure **10** and **11**, respectively.

Caution. Since F_2 is a highly oxidizing and toxic gas, any experimenter should know the precautions necessary for the safe handling of F_2.[5e]

***N,N*′-Difluoro-2,2′-bipyridinium bis(trifluoromethanesulfonate) (1a):** mp 190−193 °C (CH_3CN-Et_2O); ^{1}H NMR (CD_3CN) δ 8.74−8.58 (4 H, m), 9.01 (2H, dt, J = 7.9, 1.0 Hz), 9.70 (2H, ddd, J = 16.1, 7.0, 1.0 Hz); ^{19}F NMR 44.0 (2F, brs, N−F), −78.0 (6F, s, CF_3); IR (Nujol) 3063, 1277, 1157, 1032 cm^{-1}. Anal. Calcd for $C_{12}H_8F_8N_2O_6S_2$: C, 29.28; H, 1.64; N, 5.69. Found: C, 29.21; H, 1.41; N, 5.63.

***N,N*′-Difluoro-2,2′-bipyridinium Bis(tetrafluoroborate) (1b):** mp 166.6−167.7 °C (CH_3CN-Et_2O); ^{1}H NMR (CD_3CN) δ 8.74−8.58 (4H, m), 9.01 (2H, dt, J = 8, 1 Hz), 9.65 (2H, ddd, J = 16, 7, 1 Hz); ^{19}F NMR 43.6 (2F, brs, N−F), −150 (8F, s, BF_4); IR (Nujol) 3126, 1592, 1488, 1281, 1202, 1057 cm^{-1}; MS (EI) m/z 97 ((M − $2BF_4$)$^{2+}$/2). Anal. Calcd for $C_{10}H_8B_2F_{10}N_2$: C, 32.66; H, 2.19; N, 7.62. Found: C, 32.46; H, 2.02; N, 7.48.

***N,N*′-Difluoro-4,4′-dimethyl-2,2′-bipyridinium bis(tetrafluoroborate) (2b):** mp 153−160 °C (with dec) (CH_3CN-Et_2O); ^{1}H NMR (CD_3CN) δ 2.84 (6H, s, CH3), 8.37 (2H, dm, J = 7 Hz), 8.46 (2H, dd, J = 6, 3 Hz), 9.41 (2H, dd, J = 16, 7 Hz); ^{19}F NMR 35.7 (2F, brs, N−F), −149.8 (8F, s, BF_4); IR (Nujol) 3065, 1600, 1488, 1293, 1208, 1078, 1055, 1028, 837, 760 cm^{-1}; MS (FAB) m/z 203 (M^+ − F − $2BF_4$). Anal. Calcd for $C_{12}H_{12}B_2F_{10}N_2$: C, 36.41; H, 3.06; N, 7.08. Found: C, 36.36; H, 2.85; N, 7.34.

***N,N*′-Difluoro-4,4′-dichloro-2,2′-bipyridinium bis(tetrafluoroborate) (3b):** mp 136−140 °C (with dec) (CH_3CN-Et_2O); ^{1}H NMR (CD_3CN) δ 8.66 (2H, ddd, J = 7.5, 2.8, 1.5 Hz), 8.71 (2H, dd, J = 5.3, 2.8 Hz), 9.62 (2H, dd, J = 14.7, 7.5 Hz); ^{19}F NMR 39.3 (2F, s, N−F), −150.7 (8F, s, BF_4); IR (Nujol) 3094, 1584, 1280, 1212, 1150, 1052 cm^{-1}.

***N,N*′-Difluoro-4,4′-diphenyl-2,2′-bipyridinium bis(tetrafluoroborate) (4b):** mp 127−133 °C (with dec) (CH_3CN-Et_2O); ^{1}H NMR (CD_3CN) δ 7.68−7.83 (6H, m), 8.02−8.12 (4H, dm, J = 8 Hz), 8.78 (2H, dm, J = 8 Hz), 8.94 (2H, dd, J = 6, 3 Hz), 9.60 (2H, dd, J = 15, 8 Hz); ^{19}F NMR 33.9 (2F, brs, N−F), −149.9 (8F, s, BF_4); IR (Nujol) 1590, 1292, 1208, 1071, 1040, 765 cm^{-1}. Anal. Calcd for $C_{22}H_{16}B_2F_{10}N_2$: C, 50.82; H, 3.10; N, 5.39. Found: C, 50.14; H, 3.13; N, 6.73.

***N,N*′-Difluoro-4,4′-bis(methoxycarbonyl)-2,2′-bipyridinium bis(hexafluoroantimonate) (5d):** mp 81 °C; ^{1}H NMR (CD_3CN) δ 4.11 (6H, s), 9.03 (2H, m), 9.09 (2H, dd, J = 5.7, 2.6 Hz), 9.87 (2H, dd, J = 14.8, 7.1 Hz); ^{19}F NMR 47.7 (2F, brs, N−F), −110 to −133 (12F, m, SbF_6); IR (Nujol) 1750, 1303, 1205, 1143, 1018 cm^{-1}.

***N,N*′-Difluoro-5,5′-bis(trifluoromethyl)-2,2′-bipyridinium bis(trifluoromethanesulfonate) (6a):** mp 177−183 °C (with dec); ^{1}H NMR (CD_3CN) δ 9.08 (2H, dd, J = 8, 3 Hz), 9.40 (2H, dm, J = 8 Hz), 10.42 (2H, dm, J = 15 Hz); ^{19}F NMR 48.1 (2F, brs, N−F), −61.8 (6F, s, CF_3), −77.9 (6F, s, CF_3SO_2).

***N,N*′-Difluoro-2,4′-bipyridinium bis(trifluoromethanesulfonate) (7a):** mp 152−155 °C (CH_3CN−EtOAc); ^{1}H NMR (CD_3CN) δ 8.48 (1H, m), 8.53 (1H, ddd, J = 2.0, 7.5, 7.5 Hz), 8.70 (2H, dd, J = 7.5, 4.2 Hz), 8.90 (1H, dd, J = 7.5, 7.9 Hz), 9.50 (1H, dd, J = 7.5, 17.0 Hz), 9.58 (2H, dd, J = 7.5, 13.6 Hz); ^{19}F NMR 52.8 (1F, brs, N−F), 38.7 (1F, brs, N−F), −78.1 (6F, s, CF_3); IR (Nujol) 3033, 1268, 1154, 1034, 641, cm^{-1}. Anal. Calcd for $C_{12}H_8F_8N_2O_6S_2$: C, 29.28; H, 1.64; N, 5.69. Found: C, 29.17; H, 1.60; N, 5.73.

(22) House, H. O. *Modern Synthetic Reactions*, 2nd ed.; W. A. Benjamin, Inc.: Menlo Park, CA, 1972.

(23) Ishikura, M.; Kamada, M.; Terashima, M. *Synthesis* **1984**, 936.

***N,N′*-Difluoro-2,4′-bipyridinium bis(tetrafluoroborate) (7b):** mp 189−191 °C (with dec) (CH_3CN-Et_2O); ^{1}H NMR (CD_3CN) δ 8.42−8.57 (2H, m), 8.66 (2H, m), 8.90 (1H, m), 9.4−9.6 (3H, m); ^{19}F NMR 52.6 (1F, brs, N−F), 38.3 (1F, brs, N−F), −149.8 (8F, s, BF_4); IR (Nujol) 3114, 1604, 1580, 1484, 1455, 1432, 1377, 1271, 1256, 1196, 1062, 862 cm^{-1}; MS (FAB) *m/z* 175 ($M^+ - F - 2BF_4$), 154. Anal. Calcd for $C_{10}H_8B_2F_{10}N_2$: C, 32.66; H, 2.19; N, 7.62. Found: C, 32.76; H, 2.02; N, 7.52.

***N,N′*-Difluoro-2,4′-bipyridinium bis(hexafluorophosphate) (7c):** mp 150−159 °C (with dec) (CH_3CN-Et_2O); ^{1}H NMR (CD_3CN) δ 8.42−8.55 (2H, m), 8.63 (2H, m), 8.90 (1H, m), 9.4−9.6 (3H, m); ^{19}F NMR 52.8 (1F, brs, N−F), 38.3 (1F, brs, N−F), −71.4 (12F, d, J = 703 Hz, PF_6); IR (Nujol) 3121, 1445, 1376, 1251, 1207, 1061, 833 cm^{-1}. Anal. Calcd for $C_{10}H_8F_{14}N_2P_2$: C, 24.81; H, 1.67; N, 5.79. Found: C, 25.74; H, 1.63; N, 5.62.

***N,N′*-Difluoro-3,3′-bipyridinium bis(trifluoromethanesulfonate) (8a):** mp 129−131 °C ($CH_3CN-EtOAc$); ^{1}H NMR (CD_3CN) δ 8.52 (2H, dd, J = 7.1, 13.3 Hz), 9.00 (2H, d, J = 7.1 Hz), 9.43 (2H, dd, J = 6.8, 13.3 Hz), 9.82 (2H, d, J = 15.2 Hz); ^{19}F NMR 51.2 (2F, m, N−F), −78.0 (6F, s, CF_3); IR (Nujol) 1272 1164 1030 cm^{-1}. Anal. Calcd for $C_{12}H_8F_8N_2O_6S_2$: C, 29.28; H, 1.64; N, 5.69. Found: C, 29.28; H, 1.56; N, 5.76.

***N,N′*-Difluoro-4,4′-bipyridinium bis(trifluoromethanesulfonate) (9a):** mp 205−212 °C (with dec) (CH_3CN-Et_2O); ^{1}H NMR (CD_3CN) δ 8.63 (4H, m), 9.47 (4H, m); ^{19}F NMR 49.5 (2F, brs, N−F), −78.1 (6F, s, CF_3); IR (Nujol) 1493, 1461, 1376, 1255, 1143, 1031, 855 cm^{-1}; MS (FAB) *m/z* 175 ($M^+ - F - 2CF_3SO_3$), 154. Anal. Calcd for $C_{12}H_8F_8N_2O_6S_2$: C, 29.28; H, 1.64; N, 5.69. Found: C, 29.09; H, 1.42; N, 5.50.

***N,N′*-Difluoro-4,4′-bipyridinium bis(tetrafluoroborate) (9b):** mp 178.8−180.5 °C (CH_3CN-Et_2O); ^{1}H NMR (CD_3CN) δ 8.61 (4H, m), 9.45 (4H, m); ^{19}F NMR 49.3 (2F, m, N−F), −149.7 (8F, s, BF_4); IR (Nujol) 3113, 1604, 1307, 1256, 1197, 1059, 1028 cm^{-1}; MS (FAB) *m/z* 175 ($M^+ - F - 2BF_4$). Anal. Calcd for $C_{10}H_8B_2F_{10}N_2$: C, 32.66; H, 2.19; N, 7.62. Found: C, 32.84; H, 2.02; N, 7.55.

***N,N′*-Difluoro-4,4′-bipyridinium bis(hexafluoroantimonate) (9d):** mp 230−255 °C (with dec) (CH_3CN-Et_2O); ^{1}H NMR (CD_3CN) δ 8.58 (4H, m), 9.44 (4H, m); ^{19}F NMR 49.5 (2F, brs, N−F), −122 (12F, m, SbF_6); IR (Nujol) 3118, 1439, 1257, 854 cm^{-1}; MS (FAB) *m/z* 175 ($M^+ - F - 2SbF_6$), 154. Anal. Calcd for $C_{10}H_8F_{14}N_2Sb_2$: C, 18.04; H, 1.21; N, 4.21. Found: C, 18.20; H, 0.94; N, 4.08.

***N,N′,N″*-Trifluoro-2,2′:6′,2″-terpyridinium tris(hexafluoroantimonate) (10):** dec 85−88 °C; ^{1}H NMR (CD_3CN) δ 8.73 (2H, m), 8.81 (2H, m), 9.07 (4H, m), 9.38 (1H, t, J = 8 Hz), 9.73 (2H, ddd, J = 16, 7, 1 Hz); ^{19}F NMR 44.7 (2F, brs, N−F), 40.7 (1F, brs, N−F), −122 (18F, m, SbF_6); IR (Nujol) 3112, 1575, 1498, 1278 cm^{-1}. Anal. Calcd for $C_{15}H_{11}F_{21}N_3Sb_3$: C, 18.06; H, 1.11; N, 4.21. Found: C, 19.45; H, 1.41; N, 5.06.

Poly(*N*-fluoropyridinium hexafluoroantimonate-2,4-diyl) (11): dec 125 °C; ^{1}H NMR (D_2SO_4) δ 9.24−9.00 (2H, m), −8.47 (1H, m); ^{19}F NMR (D_2SO_4) 39.2 (1F, s, N−F), −114 to −128 (6F, m, SbF_6); IR (Nujol) 3648, 1017, 841, 722 cm^{-1}. Anal. Calcd for $C_5H_3F_7NSb$: C, 18.10; H, 0.91; N, 4.22. Found: C, 22.01; H, 1.92; N, 7.84.

Hydrolysis of *N,N′*-Difluoro-2,2′-bipyridinium bis(tetrafluoroborate) (1b). Into 30 mL of water was added with stirring 3 mmol of **1b** at room temperature. The reaction mixture was stirred at reflux temperature. The resulting precipitate was collected by filtration and dried at 110 °C under reduced pressure to give crude 6,6′-dihydroxy-2,2′-bipyridyl **12**: ^{1}H NMR ($CDCl_3/CD_3OD$ = 10/1) δ 6.72 (2H, d, J = 8.6 Hz), 7.17 (2H, d, J = 7.1 Hz), 7.68 (2H, dd, J = 8.6, 7.1 Hz). The crude solid **12** was esterificated with 6 mL of acetic anhydride in 6 mL of pyridine for 1 h at 100 °C. The reaction mixture was poured into 100 mL of cold water. The resulting precipitate was collected by filtration and dried at 150 °C under reduced pressure to give 0.649 g (80% from **1b**) of 6,6′-diacetoxy-2,2′-bipyridyl **13**.

6,6′-Diacetoxy-2,2′-bipyridyl (13): mp 177−188 °C; ^{1}H NMR ($CDCl_3$) δ 2.39 (6H, s, Ac), 7.11 (2H, d, J = 8.0 Hz), 7.90 (2H, t, J = 8.0 Hz), 8.38 (2H, d, J = 8.0 Hz); IR (KBr) 1754 (C=O) cm^{-1}; MS *m/z* 272 (M^+). Anal. Calcd for $C_{14}H_{12}N_2O_4$: C, 61.76; H, 4.44; N, 10.29. Found: C, 61.73; H, 4.37; N, 10.28.

Controlled Fluorination of 2-Acetylcyclohexanone (15) with *N,N′*-Difluoro-bipyridinium Triflates 1a, 7a, 8a, 9a, or *N*-Fluoropyridinium Triflate (14). Into a stirred solution of 1 mmol of **15** in 2 mL of acetonitrile at room temperature was added 0.5 mmol of either **1a**, **7a**, **8a**, or **9a** or 1 mmol of **14**. Each reaction was run at reflux temperature under nitrogen atmosphere and monitored at intervals by checking with a KI solution. **1a**, **7a**, **8a**, and **9a** were each consumed at the reaction times shown in Table 2. **14** was not completely consumed even at 19 h. The yields of product **16** were determined by ^{19}F NMR of the reaction mixture using fluorobenzene as an internal standard. The results are summarized in Table 2.

^{19}F NMR Tracing Experiments of Fluorination of 2-Acetylcyclohexanone (15) with *N,N′*-Difluoro-bipyridinium Triflate 1a, 7a, 8a, or 9a or *N*-Fluoropyridinium Triflate (14). To a solution of 0.063 mmol of **1a**, **7a**, **8a**, or **9a** or 0.125 mmol of **14** and 0.125 mmol of fluorobenzene in 0.8 mL of CD_3CN in a NMR tube was added 0.125 mmol of **15**, and the tube was sealed. Each sealed NMR tube was set in a NMR probe controlled at 50 °C, and each reaction was monitored at intervals by ^{19}F NMR using fluorobenzene as an internal standard. The formation curves (vs time) of product **16** are shown in Figure 2.

Fluorination of Various Nucleophiles with *N,N′*-Difluoro-2,2′-bipyridinium bis(tetrafluoroborate) (1b). General Procedure. Under N_2 atmosphere, **1b** was added to a stirred solution of a nucleophile in a solvent. Nucleophiles, solvents, additives, their amounts, reaction times, temperatures, and presence or absence of the additives are shown in Table 3. For all runs, **1b** was consumed at the reaction times shown in Table 3. For runs 1−4 and 10−15, the yields were determined by ^{19}F NMR of the reaction mixture using fluorobenzene as an internal standard. For runs 5−9, after 5 mL of 0.5 M aqueous $Na_2S_2O_3$ solution was added to the reaction mixture, the mixture was extracted with Et_2O. The extract was washed with saturated aqueous NaCl solution, dried with anhydrous $MgSO_4$, and then analyzed by ^{19}F NMR (fluorobenzene as an internal standard) and/or GC (tridecane or heptadecane as an internal standard). The fluoro products and their yields are summarized in Table 3.

A structural assignment of the products was carried out by spectral analysis or by comparison with those of authentic samples. The spectral data agreed with the assigned structures or the data of authentic samples. In run 10, 4-fluororesorcinol as a main product was separated from other fluoro products by column chromatography on SiO_2, but 4,6-difluoro- and 2-fluororesorcinol as minor products failed to be separated from each other. 4,6-Difluororesorcinol as a new compound was assigned by complete analysis of 500 MHz NMR and GC−MS: ^{1}H NMR (acetone-d_6) δ 6.66 (1H, t, J = 8.7 Hz), 6.95 (1H, t, J = 10.7 Hz), 8.11 (2H, brs); ^{19}F NMR −149.6; Millimass Found *m/z* 146.017 47. Calcd for $C_6H_4O_2F_2$ 146.017 94.

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