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Electrophilic fluorination with *N,N′*-difluoro-2,2′-bipyridinium salt and elemental fluorine

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Abstract

N,N′-Difluoro-2,2′-bipyridinium bis(tetrafluoroborate) (MEC-31) was shown to be a highly reactive electrophilic fluorinating agent with the highest effective fluorine content in its class. We have developed the perfect recycled fluorination system with MEC-31 for the lower-cost industrial fluorination and for an environment. MEC-31 can be completely recycled including the counter-anion. We found the fluorination of 2-naphthol in liquid CO_2 with MEC-31 in the presence of catalytic amount of NaOTf proceeded quantitatively without the generation of by-product.

In the fluorination of 1,3-dicarbonyl compounds with elemental fluorine, we found the introduction method of fluorine gas would be very important in order to make a reaction efficient. As fluorination goes on, the quantity of 1,3-dicarbonyl compounds of the starting material is reduced gradually, and therefore the quantity of fluorine must be reduced by the method to control the flow rate or the concentration of fluorine gas diluted with nitrogen, together the fluorination to proceed efficiently.
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Keywords: Fluorination; Fluorinating agent; Electrophilic; *N,N′*-Difluoro-2,2′-bipyridinium salt; *N*-Fluoropyridinium salt; Fluorine; Recycle; 1,3-Dicarbonyl compounds

1. Introduction

When introducing fluorine atoms to organic compounds, the characteristics of the original compound changes considerably, due to its high electronegativity, strong bonding forces with carbon, and lipophilicity effect, etc. By utilizing the peculiar characteristics of the fluorine atom, recently the introduction of fluorine into the fields of medicine, agricultural chemicals, and new materials such as liquid crystals is widely practiced.

We have been trying to advance various technical developments in order to introduce fluorine atoms into organic compounds, and have classified these technologies into fluorinating agents for researching new compounds and industrial fluorination technologies.

Fluorinating agents for researching new compounds are safe, easy to handle, and widely used agents. By using our agents for the direct fluorination of developing compounds, various fluorocompounds are able to be easily obtained, and research can proceed more rapidly than developing a new synthesis route for the fluorocompounds. At present, we have *N,N′*-difluoro-2,2′-bipyridinium bis(tetrafluoroborate) (MEC-31) [1], counter-anion-bound fluorinating agents (MEC-01, -02, -03, -04B, -05) as an electrophilic fluorinating agent [2]. Besides these agents, a lot of electrophilic fluorinating agents with an N–F moiety are known [3,4] (Scheme 1).

And we have the corresponding industrial fluorination technologies, elemental fluorine [5,6], IF_5/Et_3N-3HF [7,8], and SF_4 [9–11], for bulk supply of the new fluorocompounds that are synthesized with the fluorinating agents for researching new compounds.

Hereunder, we would like to explain fluorinating agents for researching new fluorocompounds, MEC-31, and direct fluorination with elemental fluorine for industrial fluorination technology.

2. Results and discussion

2.1. Powerful electrophilic fluorinating agent: MEC-31 (*N,N′*-difluoro-2,2′-bipyridinium bis(tetrafluoroborate))

2.1.1. Synthesis of MEC-31

MEC-31 can be synthesized in one pot by introducing BF_3 gas into 2,2′-bipyridine at 0 °C and then by introducing

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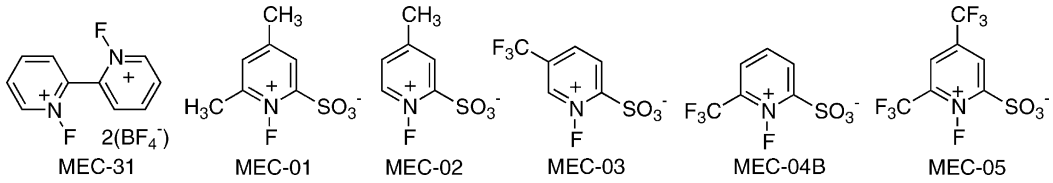
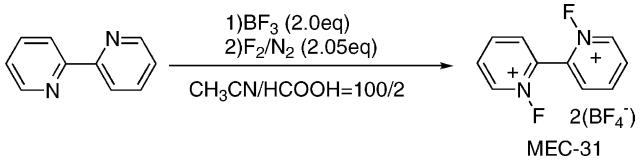


Scheme 1.



Scheme 2.

fluorine gas diluted with nitrogen to 25 vol.%. MEC-31 can be separated easily by filtration alone, because it has the characteristic of being able to crystallize well and it is created as precipitated crystals during the reaction. The isolation yield is 89% (Scheme 2).

2.1.2. Fluorination of various nucleophiles with *N,N′*-difluoro-2,2′-bipyridinium salts

MEC-31 is a stable crystal without explosive features and its melting point is 166–168 °C with decomposition. Fluorination can be performed in a glass reactor, and it is easy to remove *N,N′*-dihydro-2,2′-bipyridinium bis(tetrafluoroborate) generated after the reaction, from desired fluorinated compounds, as the salt is dissolved in diluted hydrochloric acid. As shown in Table 1, *N,N′*-difluoro-2,2′-bipyridinium salts can be applied to the fluorination of various kinds of substrates. They have the tendency to bring good results, in yield and selectivity, etc. to the aryl compounds and enol ether compounds. It is understood that as the structures of *N,N′*-difluoro-2,2′-bipyridinium salts include electron-deficient aromatic ring, they will form the π-complex with the compounds which are rich in electrons.

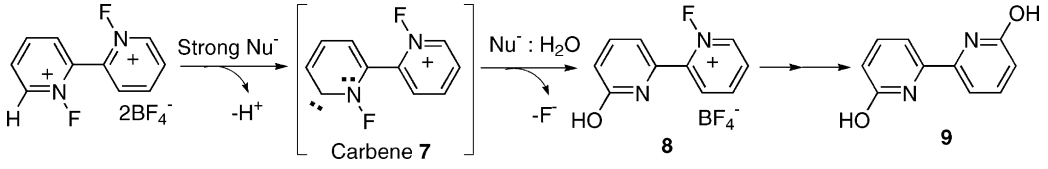
We have to note, however, the fact that the mechanism of carbene formation causes the decomposition of MEC-31 and the fluorination of substrates does not proceed, when we use highly reactive nucleophiles or solvents which have highly nucleophilic nature (such as water or DMSO, etc.), as shown in Scheme 3 [12,13]. At first, the absorption of hydrogen at the *ortho* position occurs by highly reactive nucleophiles to generate the carbene **7**. The carbene **7** reacts with nucleophiles to form 3,3'-substituted 2,2′-bipyridine derivatives. When the nucleophile is water, 3,3′-dihydroxy-2,2′-bipyridine **9** was generated in high yield (Scheme 3).

2.1.3. Effect of additive: sodium trifluoromethanesulfonate

If the reaction is slow, the addition of catalytic amount of sodium trifluoromethanesulfonate is very effective. Depending on the counter-anions of the salt, the solubility of MEC-31 into organic solvents increases remarkably, and there are cases where the reaction time is shortened for some substrates as shown in Table 2.

2.1.4. Comparison with other isomers

MEC-31 has a molecular structure of the two *N*-fluoropyridinium salts combined at the *ortho* position, and through this combination, we succeeded in enhancing the fluorinating power greatly. Fig. 1 shows the formation curves of fluorocompound **2** for the comparison of the reactivity of each *N,N′*-difluorobipyridinium bis(triflate), through the fluorination of 2-acetylcyclohexanone **1**. The reaction was done in CD_3CN at 50 °C in NMR tube and the yield of **2** was determined by ^{19}F NMR using fluorobenzene as an internal standard. A volume of 0.5 mmol of *N,N′*-difluorobipyridinium bis(triflate) was used for the fluorination of 1 mmol of the substrate **1**. In the case of *N*-fluoropyridinium triflate **13**, 1 mmol was used for 1 mmol of the substrate **1**. From this result, relative reactivity was determined to be **4** > **10** > **11** ≅ **12** ≫ **13**. The lowest reactivity of the 4,4′-isomer **12**, which has strong π-electron conjugation effect, indicates the π-electron conjugation effect to be unessential for fluorination. The highest reactivity of the 2,2′-isomer **4** would be due to the N–F moieties being the most deficient in electrons by the strong electron-withdrawing effect of other *N*-fluoropyridinium moieties in the *ortho* position at a close distance. In isomers (**10**–**12**) except the 2,2′-isomer **4**, though the reactivity of the first fluorine atom was relatively high, the reactivity of the second fluorine atom decreased remarkably, as is shown in Fig. 1, it is the same level as *N*-fluoropyridinium triflate **13**. On the other hand, in the case of 2,2′-isomer **4**, the difference of reactivity between the first and second fluorinations was very small. *N*-Hydropyridinium moiety generated after the first fluorination is less electron-withdrawing than *N*-fluoropyridinium moiety. But,



Scheme 3.

Table 1
Fluorination of various nucleophiles with *N,N′*-difluoro-2,2′-bipyridinium salt

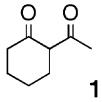
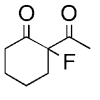
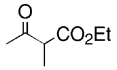
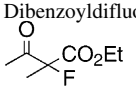
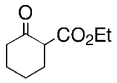
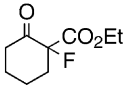
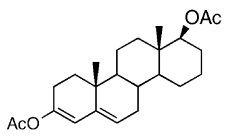
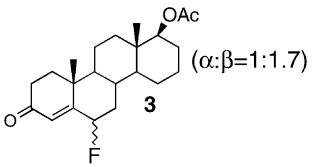
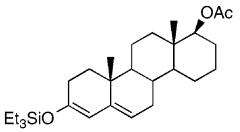
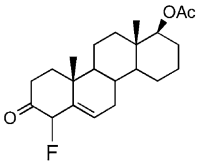
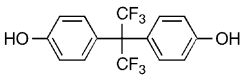
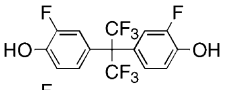
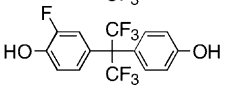
Run[a]	Nucleophile	Salt of "F"	Additive (mmol)	Solvent	Conditions	Product	Yield (%)[b]
1	 **1**	BF_4^- (MEC-31)	None	CH_3CN	Reflux, 3 h	 **2**	71
2	**1**	BF_4^-	NaOTf (0.1)	CH_3CN	Reflux, 10 min	**2**	82
3	Dibenzoylmethane	BF_4^-	TfOH (0.1)	CH_3CN	Reflux, 48 h	Dibenzoylfluoromethane Dibenzoyldifluoromethane	10 76
4		BF_4^-	None	CH_3CN	Reflux, 8 h		73
5		BF_4^-	None	CH_3CN	Reflux, 8 h		76
6	Phenol	BF_4^-	None	CH_3CN	Reflux, 8 h	*o*-Fluorophenol *p*-Fluorophenol 2,4-Difluorophenol	39 33 5
7	Phenol	BF_4^-	NaOTf (0.1)	CH_3CN	Reflux, 5 h	*o*-Fluorophenol *p*-Fluorophenol 2,4-Difluorophenol	39 31 6
8	Anisole	BF_4^-	None	CH_3CN	Reflux, 9 h	*o*-Fluoroanisole *p*-Fluoroanisole 2,4-Difluoroanisole	40 28 8
9	Phenylurethane	BF_4^-	None	CH_3CN	Reflux, 48 h	*o*-Fluorophenylurethane *p*-Fluorophenylurethane 2,4-Difluorophenylurethane	48 32 5
10	Resorcinol	BF_4^-	None	CH_3CN	Reflux, <5 min	4-Fluroresorcinol 4,6-Difluroresorcinol 2-Fluroresorcinol	72 10 3
11	2-Naphthol	BF_4^-	None	HCOOH	RT, 10 min	1-Fluoro-2-naphthol 1,1-Difluoro-2-naphthalenone	61 18
12	*trans*-PhCH=CHCH$_3$	BF_4^-	None	AcOH	Reflux, <15 min	PhCH(OAc)CHFCH$_3$	51
13	2-Tetralone	BF_4^-	None	CH_3CN	Reflux, <10 min	1-Fluoro-2-tetralone	38
14		BF_4^-	$NaHCO_3$ (0.25)	CH_3CN	70 °C, 1 h	 (α:β=1:1.7) **3**	82

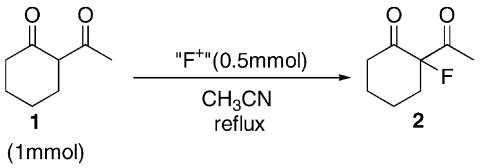
Table 1 (*Continued*)

Run[a]	Nucleophile	Salt of "F"	Additive (mmol)	Solvent	Conditions	Product	Yield (%)[b]
15		BF_4^-	$NaHCO_3$ (0.25)	CH_3CN	RT, 30 min	**3** + (α:β=1:1.4) 	65
16	4-Chlorophenol	TfO^- (**4**)	None	$ClCH_2CH_2Cl$	82 °C, 20 h	4-Chloro-2-fluorophenol	40
17	Methyl 4-hydroxy-benzoate	TfO^-	None	$ClCH_2CH_2Cl$	82 °C, 20 h	Methyl 3-fluoro-4-hydroxy-benzoate	50
18		TfO^-	None	$ClCH_2CH_2Cl$	82 °C, 20 h		58
							23

[a] Runs 1–15 [1]. For runs 16 and 17, the reaction was carried out in 2 ml of 1,2-dichloroethane using 0.5 mmol of a nucleophile and 0.6 mmol of *N,N′*-difluoro-2,2′-bipyridinium bis(trifluoromethanesulfonate). For run 18, the reaction was carried out in 2 ml of 1,2-dichloroethane using 0.5 mmol of a nucleophile and 0.3 mmol of *N,N′*-difluoro-2,2′-bipyridinium bis(trifluoromethanesulfonate).

[b] Determined by ^{19}F NMR using fluorobenzene as an internal standard, based on the amount of a nucleophile used.

Table 2
Effect of catalytic amount of NaOTf



"F$^+$"		Additive	Time	Yield of **2** (%)[a]
	**4**	–	<5 min	85
MEC-31		–	3 h	71
MEC-31		NaOTf (20 mol%)	10 min	82

[a] Determined by ^{19}F NMR using fluorobenzene as an internal standard.

as *N*-hydropyridinium moiety exerts a fairly strong electron-withdrawing effect at the nearest *ortho* position, the reactivity of the second fluorine in only 2,2′-isomer **4** will be kept too high. Therefore, only the 2,2′-isomer **4** can be used in reactions with high reactivity for both fluorine atoms in the molecule.

2.1.5. Effective fluorine content: comparison with other fluorinating agents

We compared the effective fluorine content of MEC-31 with that of other electrophilic fluorinating agents having an almost equivalent reactivity with MEC-31. The effective fluorine content means the value of fluorine atoms used for reactions divided by molecular weight. This value is an indication for evaluating the cost-effective industrial fluorination. MEC-31, as stated above, has two active fluorine atoms in the molecule keeping high reactivity and, therefore, shows an extremely high value of effective fluorine content per unit weight, in comparison with the other fluorinating agents as shown in Table 3.

2.1.6. Perfect recycled system in fluorination with MEC-31

We have developed the perfect recycled system with MEC-31 for the lower-cost industrial fluorination and for an environment. MEC-31 can be completely recycled including the counter-anion as shown in Fig. 2. After the fluorination of 2-naphthol at 88% yield, MEC-31 itself is collected quantitatively in the form of *N,N*′-dihydro-2,2′-bipyridinium bis(tetrafluoroborate) (**16**). The salt **16** is easily collected through filtration, due to good crystallization and low solubility in solvents. The salt **16** can almost be quantitatively converted to MEC-31 again by fluorine gas and can be used for the fluorination of substrates without isolation. We consider this fluorination system by recycling MEC-31 as a form of fluorination technology for the next generation, since it has less impact on the environment.

2.1.7. Fluorination with *N,N*′-difluoro-2,2′-bipyridinium salts in liquid carbon dioxide

The reaction using carbon dioxide as a solvent, which is nonpoisonous, and nonflammable which is extremely safe,

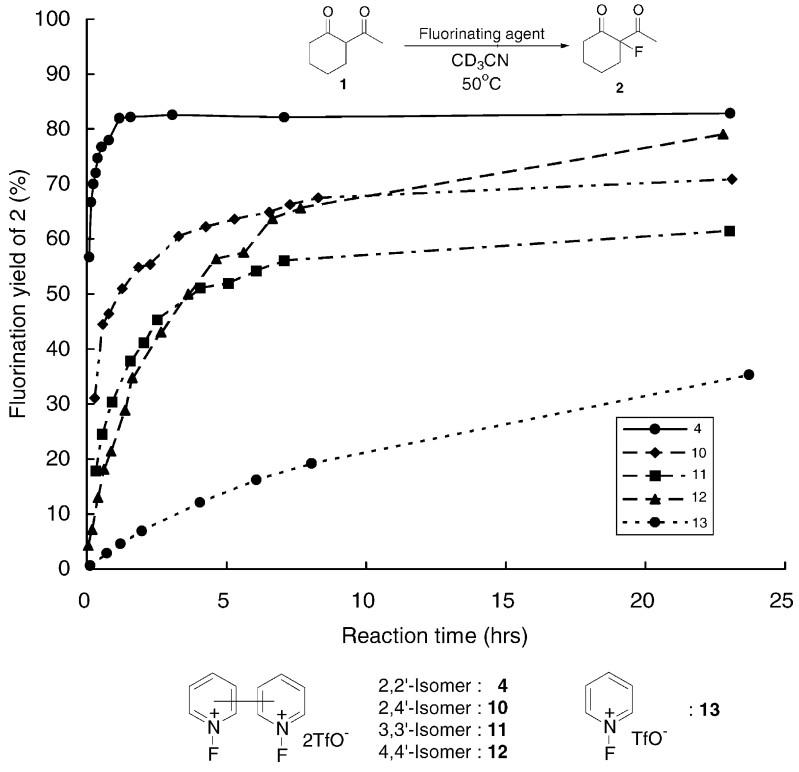
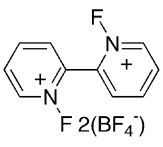
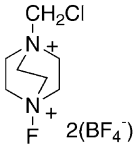
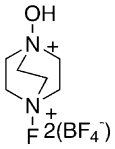
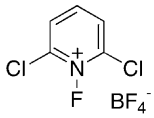


Fig. 1. Comparison of reactivity with other isomers.

Table 3
Comparison of effective fluorine content

	Molecular structure (trade name)			
	 (MEC-31)	 (Selectfluor)	 (Accufluor NFTh)	 (FP-B800)
Molecular weight	367.8	354.3	321.8	253.8
Effective fluorine content (g/kg)	103	54	59	75

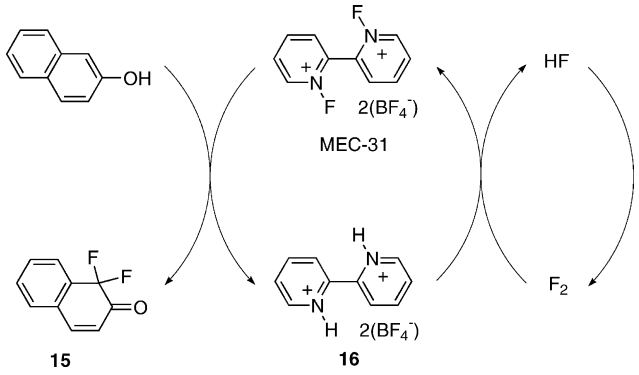


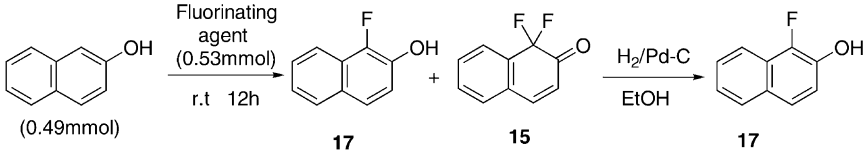
Fig. 2. Perfect recycled system in fluorination with MEC-31.

easily eliminated, and easily recovered, is considered to be excellent due to being gentle to environment just like non-solvent reaction.

The methods of using molecular fluorine, xenon difluoride, and $CF_3CHFCF_2N(C_2H_5)_2$ are reported, in fluorination with carbon dioxide as a solvent [14]. It is reported that fluorination of saturated hydrocarbon using xenon difluoride proceeds at 30% yield under the violent conditions of 105 °C and 5000 psia (340 atm). There is, however, no example of the fluorination in carbon dioxide using electrophilic fluorinating agent that has N–F bonding.

We have tried fluorinating 2-naphthol in carbon dioxide, with *N,N′*-difluoro-2,2′-bipyridinium bis(triflate) (**4**) and MEC-31. Because *N,N′*-difluoro-2,2′-bipyridinium salt can be used as two active fluorine atoms in the molecule for a reaction, the reaction was made in such a condition using 1.1 times of a mole for 2-naphthol. The reaction was done in an autoclave at a room temperature in a pressured state for 12 h, the pressure was reduced to normal pressure and carbon dioxide was eliminated, then the yield of fluorination products was confirmed by ^{19}F NMR using fluorobenzene as an internal standard. During the reaction, the carbon dioxide was not at a super critical state but merely at a liquid state. As shown in Table 4, the products were the mixture of 1-fluoro-2-naphthol **17** and 1,1-difluoro-1H-naphthalen-2-one **15**, all of which were converted into **17** through the reduction by H_2/Pd–C. From the result of run 1, when fluorinating agent **4** was used in liquid carbon dioxide as a solvent, 1-fluoro-2-naphthol was gained almost quantitatively without the generation of by-product after the reduction. On the other hand, when fluorination is made, as usual at normal pressure using acetonitrile as a solvent, the yield was a comparatively low (85%). Raw material, 2-naphthol was not left all due to the side-reaction. We have found, in comparison with runs 1 and 2, that the fluorination reaction with *N,N′*-difluoro-2,2′-bipyridinium salt, when using liquid carbon dioxide as a solvent, was proceeding quite completely and that there was almost no sub-reactions. We also tried the fluorination of 2-naphthol in liquid carbon dioxide as well, with MEC-31, but this didn't react at all (run 3). When we added a catalytic amount of NaOTf, fluorination which proceeded smoothly with a yield of compound **17** was 95% after the reduction (run 4). The reason why MEC-31 did not react is considered that solubility to the liquid carbon

Table 4
Fluorination with *N,N′*-difluoro-2,2′-bipyridinium salts in liquid CO_2



Run	Fluorinating agent (mmol)	Solvent	Additive (mmol)	Yield of **17** (%)	Yield of **15** (%)	Yield of **17** by reduction (%)
1	**4**	CO_2	–	10	89	99
2	**4**	CH_3CN	–	30	56	85
3	MEC-31	CO_2	–	No reaction	No reaction	No reaction
4	MEC-31	CO_2	NaOTf (0.10)	Trace	95	95

dioxide was quite low, and the addition of catalyst NaOTf caused salt exchanges which increased it's solubility and proceeded the reaction smoothly.

N,N′-Dihydro-2,2′-bipyridinium salt generated after the fluorination reaction can be easily recovered almost quantitatively through filtration after dissolving fluorinated compounds with the addition of an organic solvent such as ether, etc. The recovered *N,N′*-dihydro-2,2′-bipyridinium salt can be returned to fluorinating agent again, by reacting it with fluorine gas as already stated, and it is possible to recycle.

2.2. Industrial fluorination technologies: direct fluorination with elemental fluorine

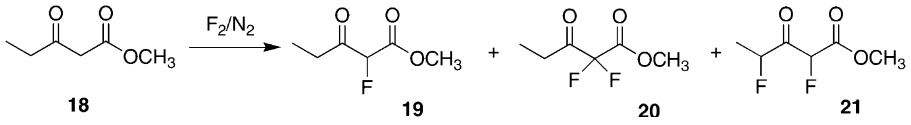
Elemental fluorine (F_2) is, needless to say, a tremendously dangerous gas due to it's reactivity, corrosiveness, poisonous characteristics, and regarding the handling of it and the control of it's reactions. Therefore, special technology and know-how is required. Elemental fluorine is, generally, not suited for the fluorination of complex compounds that contain functional groups that can be oxidized easily, but it can be used as an industrial agent for relatively simple compounds that have a clearly identified reactive site. Particularly, in the fluorination of 1,3-dicarbonyl compounds, molecular fluorine is quite effective and can achieve monofluorination in a high yield [15–18].

However, there is a problem in that the usual method in the fluorination of 1,3-dicarbonyl compounds required more excess amount of fluorine (more than 2 equivalents (eq.)) for the consumption of the starting material [15–17]. The use of more excess fluorine is not economical for the industrial production, and excess fluorine becomes not only wasteful, but also it may cause more sub-reactions. For the purpose of resolving this problem, we have studied the effect of the flow rate and the concentration of fluorine gas diluted with nitrogen and the solvent effect in the fluorination of 1,3-dicarbonyl compound [18].

2.2.1. Flow rate effect of fluorine gas

At first, we have studied the effect of the flow rate of fluorine gas diluted with nitrogen in the fluorination of methyl 3-oxovalerate (**18**) when formic acid was used as

Table 5
Comparison between constant and descending flow rate



Run	**18** (mmol)	Solvent	F_2 concentration (%)	F_2 flow rate (ml/min)	F_2 (eq.)	Time (min)	Product ratio **19**/(**19** + **18**) (%)	Yield (%)[a]		
								19	**20**	**21**
1	80	HCOOH	10	190	2.5	256	97	73	3	11
2	80	HCOOH	10	190 → 40	1.65	300	100	75	2	11

[a] Determined by ^{19}F NMR using fluorobenzene as an internal standard.

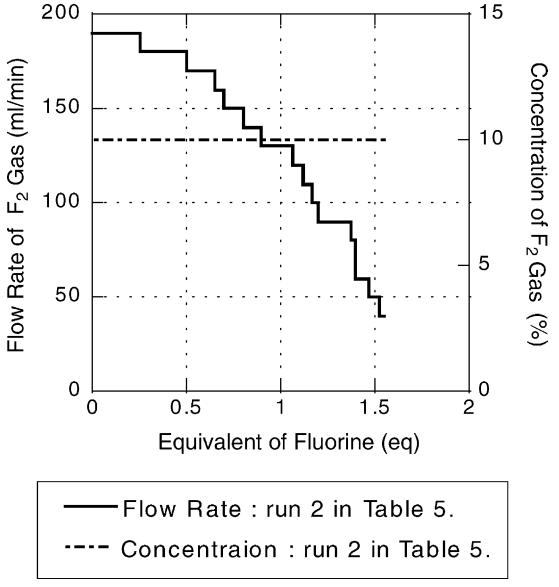


Fig. 3. Flow rate and concentration of F_2 gas at run 2 in Table 5.

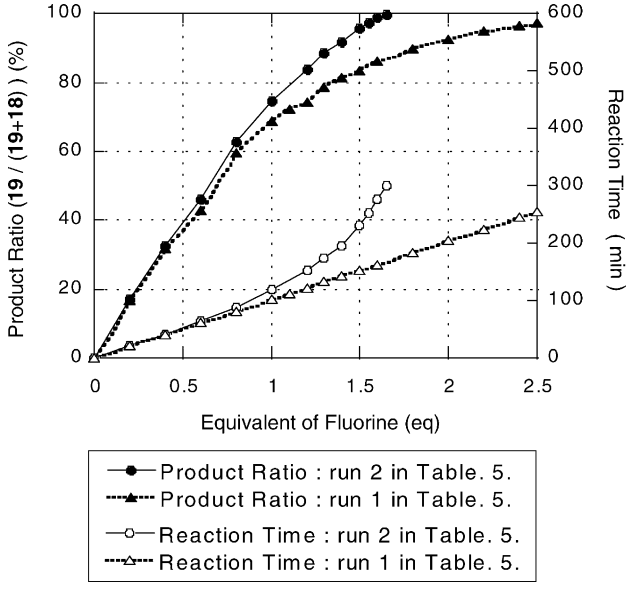


Fig. 4. Comparison between constant and descending flow rate.

a reaction solvent [18]. We have studied the relationship among the amount of introduced fluorine gas, the product ratio (percentage expressed by the ratio of a methyl 2-fluoro-3-oxovalerate (**19**) and the total quantity of **18** plus **19**, measured by gas chromatography) of the desired compound **19**, and the time required to introduce fluorine gas. We compared the fluorination of **18** at a constant flow rate and constant concentration and that at a constant concentration and descending flow rate as shown in Fig. 3, to know the flow rate effect of fluorine gas when introduced into a reaction flask. A reaction was carried out as follows: a solution of 27 ml of formic acid and dissolved starting material **18** 10.4 g (80 mmol) was cooled to 6 °C, then while stirring, 10% fluorine gas diluted with nitrogen was introduced at a constant flow rate (190 ml/min) and at descending flow rate method shown in Fig. 3. From the results shown in Table 5 and Fig. 4, we found that in run 2 at controlled flow rate we could achieve the reaction with less consumption of fluorine than that of run 2 at a constant flow rate. At constant flow rate, the starting material **18** is still remained even when 2.5 eq. of fluorine gas was introduced, and in the case of the descending flow rate method, **18** was perfectly consumed at an equivalent of 1.65 of it. As the reaction proceeded efficiently, the increment of reaction time was very small in spite of the decreased flow rate of fluorine. Table 5 shows the yield of **19** and that of by-products **20**, **21** determined by ^{19}F NMR using fluorobenzene as an internal standard. The yield of the desired compound **19** was improved a little, but a large effect in yield improvement was not confirmed. But, the complete consumption of the starting material **18** is very important for the industrial production of **19**, because, the separation of **18** from the desired compound **19** is not easy. The separation of by-products **20** and **21** is relatively easy by extraction and distillation.

2.2.2. *Concentration effect of fluorine in nitrogen gas*

Similar results were obtained by controlling the concentration of fluorine gas diluted with nitrogen. By the method shown in Fig. 5, at a constant flow rate, we compared the case where the concentrations of fluorine gas were changed in descending order with the case where the concentration of fluorine gas was kept constant. As a result, we could attain fluorination reaction more efficiently with less fluorine consumption as in run 3 in Table 6 and Fig. 5 using the descending concentration method rather than in run 1 at a constant concentration. The case of run 2 where fluorine was

Table 6
Comparison between constant and descending concentration

Run	**18** (mmol)	Solvent	F_2 concentration (%)	F_2 flow rate (ml/mm)	F_2 (eq.)	Time (min)	Product ratio **19**/(**19** + **18**) (%)	Yield (%)[a]		
								19	**20**	**21**
1	50	HCOOH	10	100	2.5	304	94	66	2	11
2	50	HCOOH	5	100	2.0	485	96	72	3	11
3	50	HCOOH	10 → 3	100	2.0	402	97	71	2	11

[a] Determined by ^{19}F NMR using fluorobenzene as an internal standard.

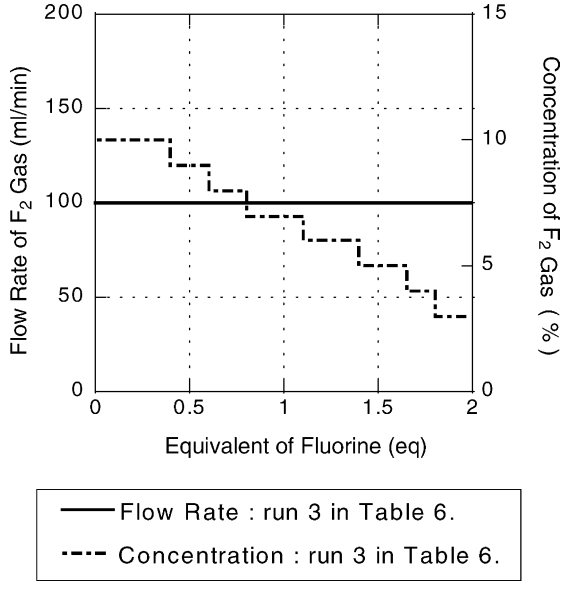


Fig. 5. Flow rate and concentration of F_2 gas at run 3 in Table 6.

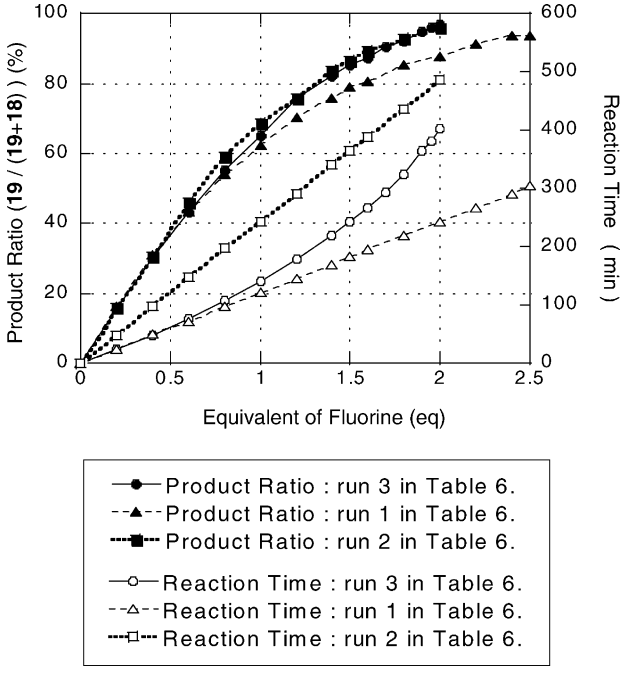


Fig. 6. Comparison between constant and descending concentration.

Table 7
Comparison of solvent effect

Run	**18** (mmol)	Solvent	F_2 concentration (%)	F_2 flow rate (ml/mm)	F_2 (eq.)	Time (min)	Product ratio **19**/(**19** + **18**) (%)	Yield (%)[a]		
								19	**20**	**21**
1[b]	80	HCOOH	10	190 → 40	1.65	300	100	75	2	11
2	80	HCOOH:CH_3CN (1:5)	10	190 → 70	1.86	258	100	61	6	21
3	80	HCOOH:CH_3CN (2:1)	10	190 → 60	1.4	189	100	80	3	15

[a] Determined by ^{19}F NMR using fluorobenzene as an internal standard.
[b] The experiment of run 1 is equal to that of run 2 in Table 5.

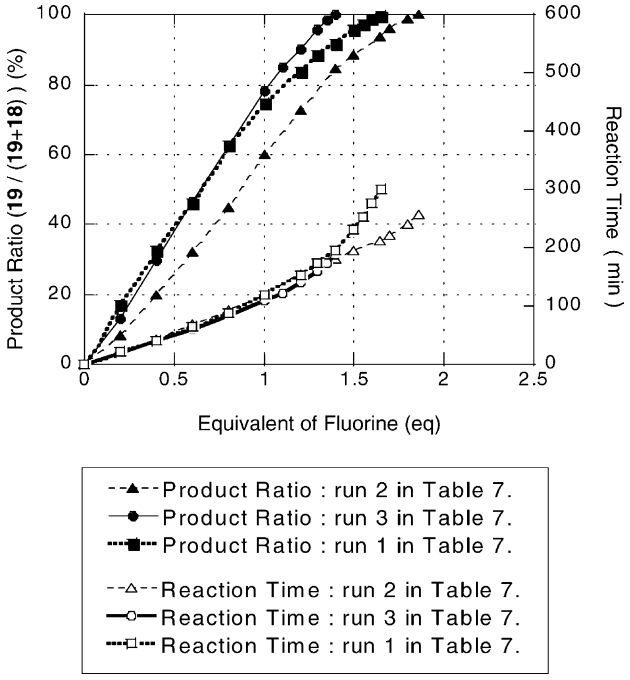


Fig. 7. Comparison of solvent effect.

introduced in thin concentrations set from the beginning at a constant quantity could attain almost the same result as in run 3, but required more reaction time and was not efficient for the industrial fluorination. Further, we observed that the descending method with the reaction proceeding, for both flow rate and concentration of fluorine gas, could also be highly effective.

From above mentioned results, we found the introduction method of fluorine gas would be very important in order to make a reaction efficient in the fluorination of 1,3-dicarbonyl compounds with elemental fluorine. As fluorination goes on, the quantity of 1,3-dicarbonyl compounds of the starting material is reduced gradually, and therefore the quantity of introduced fluorine must be reduced together the fluorination to proceed efficiently. If it is not reduced, excessively introduced fluorine becomes not only wasteful, but also it may cause more sub-reactions.

2.2.3. Solvent effect

We have studied the solvent effect in similar fluorination reactions [18]. Namely, fluorination of **18** was done, with the solvent shown in Table 7, at the almost same flow rate of descending method shown in Fig. 3 and at a constant concentration (10%) of fluorine gas. In all cases, the starting material **18** was not detected at the end of the reaction. As a result, we found that the mixed solvent of formic acid and acetonitrile by the ratio of 2:1 raised the reaction efficiency more than the single solvent of formic acid. The amount of only 1.4 eq. of fluorine was necessary for the complete consumption of **18**. Besides, the yield of the desired compound **19** increased to 80%. As observed in run 2, however, when a portion of acetonitrile was increased, the reaction efficiency was decreased, and the selectivity of the reaction was decreased due to the fact that the yield of **19** was extremely lower at 61% and the by-products **20** and **21** were increased to 6 and 21%. We, therefore, found the use of a mixed solvent with an appropriate ratio of formic acid and acetonitrile and controlling the introducing amount of fluorine gas contributed to the efficient fluorination of 1,3-dicarbonyl compound.

3. Experimental

3.1. General

^1H 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 ^1H NMR, unless otherwise noted. The ^{19}F chemical shifts were given in ppm downfield from $CFCl_3$ as an internal standard. An autoclave was used for the experiments of fluorination in carbon dioxide. GC analyses were carried out on a Shimadzu gas chromatograph with a column (2 m × 4 mm) packed with DEGS (15%) on Uniport B. The synthesis of *N,N′*-difluorobipyridinium salts and the fluorination of various nucleophiles with *N,N′*-difluorobipyridinium salts were done according to the methods stated in [1].

3.2. Fluorination with N,N′-difluorobipyridinium salts in carbon dioxide

2-Naphthol 0.070 g (0.49 mmol) and *N,N′*-difluoro-2,2′-bipyridinium bis(triflate) (**4**) 0.26 g (0.53 mmol) were placed in 50 ml autoclave, and were sealed under a decompressed state. It was cooled down to −70 °C, after

introducing carbon dioxide 15 g, then sealed again, and stirred for 12 h at room temperature. It was cooled to 0 °C, and carbon dioxide was discharged gradually. After water was added to the reaction mixture, the mixture was extracted with chloroform. The extract was washed with saturated aqueous NaCl solution, dried with sodium sulfate anhydride and was evaporated to dryness under reduced pressure. The residue was column chromatographed on silica gel using a 1:4 mixture of ethyl acetate and hexane as an eluent to give the mixture of 1,1-difluoro-1H-naphthalen-2-one (**15**) 783 mg (89%) and 1-fluoro-2-naphthol (**17**) 77 mg (10%), as a brown solid. The mixture 860 mg was dissolved in 3 ml of ethanol, 0.03 g of 5% Pd–C was added, and was stirred for 8 h at room temperature in the atmosphere of hydrogen. To the reaction mixture was added 3 ml of chloroform, being filtered with celite, the filtrate was evaporated to dryness under reduced pressure, to give 780 mg (99%) of 1-fluoro-2-naphthol as light yellow crystal. The spectral data were in agreement with those of an authentic sample [1].

The experiments of run 3 and 4 in Table 4 were done according to the same method stated above, except for an addition of sodium triflate (0.10 mmol) for run 4.

3.3. Fluorination of methyl 3-oxovalerate (*18*) with fluorine gas

3.3.1. Runs 1 and 2 in Table 5

The solution of methyl 3-oxovalerate (**18**) 10.4 g (80 mmol) dissolved in 27 ml of formic acid was cooled to 6 °C. Fluorine gas diluted with nitrogen to 10% was passed through the stirred reaction mixture at a constant flow rate (190 ml/min) for run 1, at a descending flow rate in accordance with the method shown in Fig. 3 and Table 8.

The product ratio of the desired compound **19** was determined by the GC analysis of the reaction mixtures and the results are shown in Fig. 4. The equivalent numbers of fluorine were calculated from the flow rate and the concentration of fluorine. In run 2, the amount of fluorine required for the complete consumption of the starting material **18** was 132 mmol (1.65 eq.), and the reaction time was 300 min. After the reaction, the yields of **19**, **20** and **21** were determined by ^{19}F NMR of the reaction mixture using 751 μl (8 mmol) of fluorobenzene as an internal standard and the results were shown in Table 5.

Table 8
Experimental procedure of run 2 in Table 5

F_2 (eq.)	Flow rate of F_2 gas (ml/min)	Concentration of F_2 gas (%)
0.00	190	10
0.25	180	10
0.50	170	10
0.65	160	10
0.70	150	10
0.80	140	10
0.90	130	10
1.06	120	10
1.12	110	10
1.17	100	10
1.20	90	10
1.37	80	10
1.40	60	10
1.47	50	10
1.52	40	10
1.65	40	10

Table 9
Experimental procedure of run 3 in Table 6

F_2 (eq.)	Flow rate of F_2 gas (ml/min)	Concentration of F_2 gas (%)
0.00	100	10
0.40	100	9
0.60	100	8
0.80	100	7
1.10	100	6
1.40	100	5
1.65	100	4
1.80	100	3
2.00	100	3

3.3.2. Runs 1–3 in Table 6

The solution of methyl 3-oxovalerate (**18**) 6.5 g (50 mmol) dissolved in 17 ml of formic acid was cooled to 6 °C. Fluorine gas diluted with nitrogen to 5% for run 2, 10% for run 1 or changing concentration in accordance with the method shown in Fig. 5 and Table 9 for run 3 was passed through the stirred reaction mixture at a constant flow rate (100 ml/min). The product ratio of **19** was determined by the GC analysis of the reaction mixtures as mentioned above and the results are shown in Figs. 6 and 7. After the reaction, the yields of **19**, **20** and **21** were determined by ^{19}F NMR of the reaction mixture using 469 μl (5 mmol) of fluorobenzene as an internal standard and the results were shown in Table 6.

3.3.3. Runs 2 and 3 in Table 7

Mixtures of formic acid and acetonitrile shown in Table 7 were used, and all the procedures were done similarly as explained for run 1 in Table 7 (run 2 in Table 5), except that the flow rates of fluorine gas were made in accordance

Table 10
Experimental procedure of run 2 in Table 7

F_2 (eq.)	Flow rate of F_2 gas (ml/min)	Concentration of F_2 gas (%)
0.00	190	10
0.20	160	10
1.00	150	10
1.30	140	10
1.70	110	10
1.80	70	10
1.86	70	10

Table 11
Experimental procedure of run 3 in Table 7

F_2 (eq.)	Flow rate of F_2 gas (ml/min)	Concentration of F_2 gas (%)
0.00	190	10
0.55	175	10
0.75	160	10
0.95	145	10
1.05	130	10
1.10	115	10
1.20	100	10
1.30	70	10
1.38	60	10
1.40	60	10

with the method shown in Table 10 for run 2 and Table 11 for run 3.

4. Conclusions

In the above, we have introduced our current fluorination technologies. We succeeded in the development of high reactive fluorinating agent MEC-31 having high effective fluorine content by coupling double *N*-fluoropyridinium salt at *ortho* position. And we found that MEC-31 can be recycled easily for the lower-cost industrial fluorination and for an environment. Besides that, the corresponding industrial fluorination technologies are being sufficiently developed such as the direct fluorination of 1,3-dicarbonyl compounds with fluorine gas as mentioned above.

We are hopeful that new useful fluorocompounds in various fields will be born through our fluorination technologies.

Acknowledgements

The early study of MEC-31 and the fluorination of 1, 3-dicarbonyl compounds with fluorine gas were executed under the direction of Dr. Teruo Umemoto during his term of office in Daikin Industries Ltd.

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