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General and Highly Efficient Syntheses of *m*-Fluoro Arenes Using Potassium Fluoride-Exchange Method[1)]

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Tetraphenylphosphonium bromide was found to be a suitable catalyst for the reaction of *m*-nitroaryl derivatives carrying cyano, nitro, chlorocarbonyl, trifluoromethyl, and chlorosulfonyl groups with potassium fluoride in the presence of a stoichiometric amount of phthaloyl dichloride, giving the corresponding *m*-fluoro aromatic derivatives in good yields. The catalyst was also found to be efficient for the fluorodesulfonylation of *m*-(fluorosulfonyl)aryl derivatives to afford *m*-fluoro arenes by the use of a reaction-distillation technique.

Fluorine-containing aromatic compounds are of current interest because of their unique chemical and biological properties in agricultural and pharmaceutical research areas.[2)] Although a number of methods for the introduction of fluorine into organic molecules have been developed and successfully utilized for the synthesis of fluoro aromatic compounds,[3)] halogen-exchange reactions of the corresponding chloro aromatic compounds by potassium fluoride (KF) seem to be one of the most practical and useful methods.[4)] This method is, in general, useful for chlorine placed at *ortho*- and/or *para*-positions to electron-withdrawing groups such as NO_2, CN, CF_3, and COCl, giving *o*- and/or *p*-fluoro aromatic derivatives in fairly good yields. However, the limitation of this method is that the reaction of *m*-chloro aromatic compounds without any other substituent as activating chlorine with KF gave poor results. For example, Ishikawa reported that a reaction of 1-chloro-3-nitrobenzene (**1i**) with KF in dimethyl sulfoxide (DMSO) did not afford 1-fluoro-3-nitrobenzene (**2a**) at 190 °C.[5)]

Although numerous attempts to enhance the nucleophilicity of fluoride ion on halogen-exchange reactions have been made for the syntheses of fluoro aromatic compounds (spray-dried KF,[6)] freeze-dried KF,[7)] KF/18-crown-6 complex,[8)] KF/CaF_2,[9)] AgF/CaF_2,[10)] Ph_4PHF_2,[11)] Ph_4PBr/KF,[12)] Ph_4PBr/18-crown-6/KF,[13)] PEG/KF,[14)] Ph_4PBr/PEG/KF,[15)] polystyrene-supported pyridinium salt/KF[16)]), efficient methods for the preparation of *m*-fluoro aromatic compounds by KF-exchange are quite few. Kumai and co-workers[17)] recently reported in a patent that 3-fluorobenzonitrile (**2b**) was obtained from 3-chlorobenzonitrile in 31% GLC yield by a halogen-exchange reaction in the presence of 1-(2,2-dimethylpropyl)-4-(dimethylamino)pyridinium chloride[18)] as a catalyst. A direct replacement of *m*-substituted aryl chloride to *m*-substituted aryl fluoride by halogen-exchange seems to be very difficult.

However, a leaving group displaced by fluoride ion is not always only chloride with the aim of preparation of fluoro arenes. Actually, several successful results were reported for the preparation of *o*- and/or *p*-fluoro arenes by fluorodenitrations.[19)] For the preparation of *m*-fluoro aromatic compounds, the use of fluorodenitrations[20—22)] and fluorodesulfonylations[23)] have also been reported. However, these reactions do not generally seem to be applicable to the large scale preparation of *m*-fluoro arenes, due to the rather low yields, the long reaction time taken even in polar solvents at elevated temperatures, and the limitation of the applicable compounds.

We have now found that tetraphenylphosphonium bromide (Ph_4PBr) is a quite promising catalyst for this purpose, and that a number of *m*-nitro- and *m*-fluorosulfonyl aromatic compounds carrying such functional groups as NO_2, CN, COCl, and CF_3 can readily be converted to the corresponding *m*-fluoro arenes in good yields.[1)] This report deals with the details of these findings.

Results and Discussion

Fluorodenitrations. In order to compare the catalytic efficiency for fluorodenitration, we chose the conversion of 3-nitrobenzonitrile (**1b**) to **2b** (Eq. 1). This nitro derivative has a reasonable tendency to undergo substitution and produces a single fluoro aromatic product.

(1)

1b **2b**

In the absence of a catalyst, a tetrahydrothiophene 1,1-dioxide (sulfolane) solution of **1b** afforded no detectable **2b** after vigorous stirring with spray-dried KF (2 equiv) for 5 h at 210 °C. In the presence of 0.1 equiv of Ph_4PBr, a 10% yield of **2b** was obtained with a 33% conversion of **1b**. Surprisingly, when phthaloyl dichloride (PDC) (1 equiv) was employed, **2b** was produced in an 86% isolated yield, in which case phthalic anhydride was obtained in an almost quantitative yield. Table 1 lists the observed results in the presence or absence of Ph_4PBr and PDC. As 2 equiv of KF was consumed to react with PDC (PDC

Table 1. Reaction of 3-Nitrobenzonitrile (**1b**) with Spray-Dried Potassium Fluoride in the Presence or Absence of Tetraphenylphosphonium Bromide and Phthaloyl Dichloride[a]

Run	KF	Ph_4PBr	PDC	Reaction time/h		Conv. of **1b**	Yield of **2b**
	equiv	equiv	equiv	At 150 °C	then 210 °C	%	%
1	2.0	0	0	0	5	0	0
2	2.0	0.1	0	2	3	33	10[b]
3	2.2	0.1	1.0	2	4	30	23
4	4.0	0.1	1.0	2	2	98	86

a) See experimental part. b) Accompanied by 21% of bis(3-cyanophenyl) ether.

Table 2. Efficiency of Tetraphenylphosphonium Bromide as Catalyst

Run	KF	Catalyst	PDC	Reaction time/h		Conv. of **1b**	Yield of **2b**[a]
	equiv	0.1 equiv	equiv	At 150 °C	then 210 °C	%	%
1	4.0	no	1.0	2	4	6	6
2	the resulting mixture of run 1 plus 0.1 equiv of Ph_4PBr			0	4.5	98	81
3	4.0	Me_4NCl	1.0	2	8	29	12

a) Yields were determined by GLC.

was converted to phthaloyl difluoride (PDF)) before fluorodenitration of **1b**, excess of KF is necessary on the reaction. When a slight excess of KF was employed, the reaction did not proceed smoothly. Regarding the standard procedure, 4 equiv of KF and 1 equiv of PDC were employed (Table 1, Run 4).

In order to confirm the efficacy of Ph_4PBr on the reaction, similar treatments were carried out again. Thus, a mixture of **1b** (1 equiv), KF (4 equiv), and PDC (1 equiv) was heated. As expected, both the conversion and the yield were only 6% (Table 2, Run 1). To the mixture was added 0.1 equiv of Ph_4PBr; the resulting mixture was further stirred at 210 °C for 4.5 h. Analysis of the organic layer revealed an 81% yield of **2b** (Table 2, Run 2). When tetramethylammonium chloride (Me_4NCl)[19a] was used as a catalyst instead of Ph_4PBr, only a 12% yield of **2b** was obtained after 10 h.

The precise reaction mechanism of the novel catalytic reaction is presently obscure. However, we have already observed that the reaction of **1b** with KF in the presence of Ph_4PBr plus PDC produced **2b** exclusively. We presumed that Ph_4PBr accelerates Eq. (a) in Scheme 1.1 to enhance the nucleophilicity of fluoride ion.[12,13] The role of PDC might be a trapping agent of potassium nitrite (KNO_2) and/or dipotassium oxide (K_2O) generated from thermal decomposition of KNO_2 at 210 °C.[19a,24] In the absence of PDC, the generation of a brown gas (presumably nitrogen dioxide) was observed; the resulting mixture was very messy to produce high boiling or tarry materials which might be derived from KNO_2 or K_2O. The main by-product was identified as bis(3-cyanophenyl) ether (Ar_2O) which might be derived from a nucleophilic attack of K_2O to **2b**. Analysis of the resulting mixture of the experiment in Table 1, Run 2, revealed the production of Ar_2O in a 21% yield.

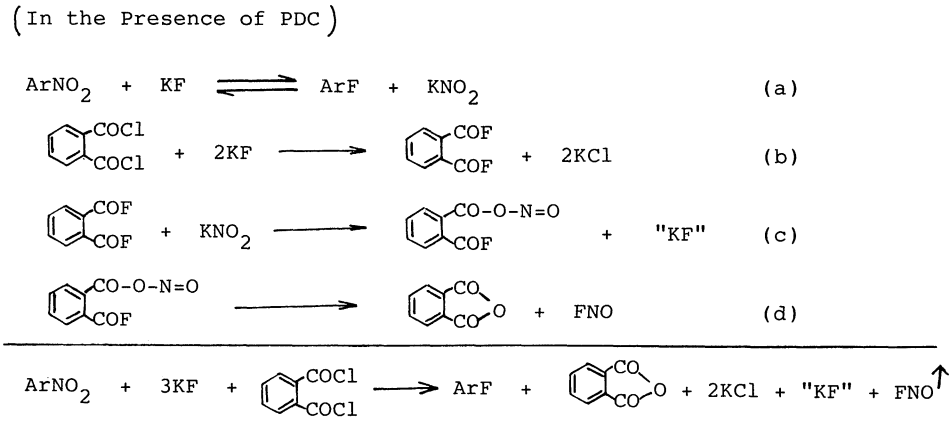
Table 3. Fluorodenitration of 1,3-Dinitrobenzene (**1a**) under Various Conditions[a]

Run	KF	PDC	Conv.	Yield of **2a**[b]
	equiv	equiv	%	%
1	1.2	0	29	16
2	2.2	0	29	20
3	2.2	0.5	61	45
4	2.2	1.0	29	26
5	3.2	1.0	95	93

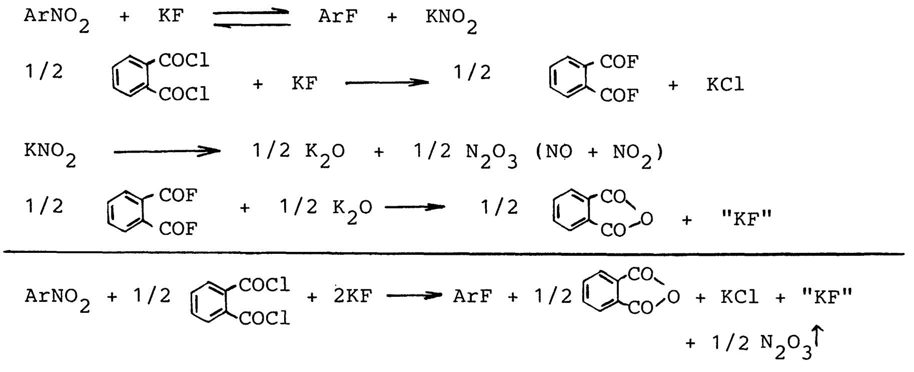
a) Ph_4PBr (0.1 equiv) was used. All reactions were performed at 150 °C for 2 h then at 180 °C for 2 h. b) GLC analysis using internal standard technique.

In order to further examine the effect of PDC, several control experiments were carried out, as shown in Table 3. The fluorination reaction, consequently, proceeded smoothly in the presence of 3 equiv of KF and 1 equiv of PDC (Table 3, Run 5). In this case, phthalic anhydride was produced in quantitative yield, confirmed by GC-MS (*m*/*z* 148). Considering these facts, this reaction has been best explained as shown in Scheme 1.1. Stoichiometrically, 2 equiv of KF should be reasonably used. However, one more excess of KF was required for the completion of the reaction (Table 3, Runs 4 and 5). We are tentatively thinking that the "KF" regenerated in Eq. (c) does not have any fluorination ability.[25]

We first considered a path including the thermal decomposition of KNO_2 (Scheme 1.2). However, it does not seem to be reasonable from the results of the control experiments mentioned above. The reaction did not come to completion in the presence of 2 equiv of KF and 0.5 equiv of PDC (Table 3, Run 3). In the case of absence of PDC, the path shown in Scheme 2.1 could be reasonable.



Scheme 1.1.



Scheme 1.2.

(In the Absence of PDC)

$$\mathrm{ArNO_2 + KF \rightleftharpoons ArF + KNO_2}$$
$$\mathrm{KNO_2 \longrightarrow 1/2\,K_2O + 1/2\,N_2O_3}$$
$$\mathrm{1/2\,ArF + 1/2\,K_2O \longrightarrow 1/2\,ArOK + 1/2\,KF}$$
$$\mathrm{1/2\,ArOK + 1/2\,ArF \longrightarrow Ar_2O + 1/2\,KF}$$

Scheme 2.1.

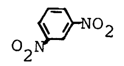
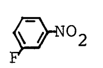
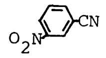
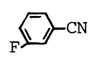
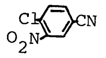
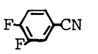
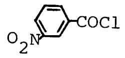
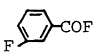
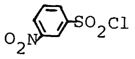
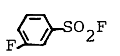
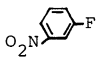
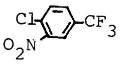
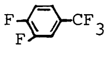
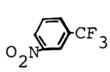
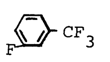
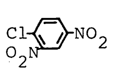
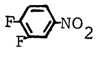
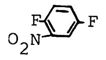
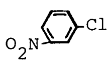
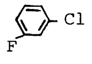
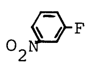
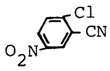
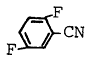
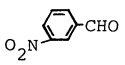
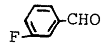
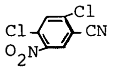
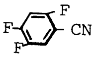
The synthetic utility of the explored fluorodenitration is further demonstrated in Table 4 by the successful fluorination of a series of aromatic compounds carrying cyano, nitro, trifluoromethyl, chlorocarbonyl, and chlorosulfonyl groups. Monosubstituted *m*-nitrobenzene derivatives such as **1a** and **1b** could be readily converted to *m*-fluoro derivatives (**2a** and **2b**) in excellent yields. In the case of **1d** and **1e**, the yield of products **2d** and **2e** would be depressed, since **2d** and **2e**, themselves, may be employed as a part of the trapping agents for KNO_2 or K_2O, even in the presence of PDC. In the case of **1g**, product **2g** is a very volatile compound, so that a considerable amount of **2g** may be uncaught during the fluorination reaction.

Fluorodesulfonylations. The authors have explored an efficient synthesis of *m*-fluoro aromatic compounds in which the fluorodenitrations catalyzed by Ph_4PBr constitutes the key reaction. Although we succeeded in preparing several *m*-fluoro aromatic congeners which have been difficult to easily prepare by employing the developed catalytic reaction, a much more efficient and practical synthesis of *m*-fluoro arenes is highly desirable because: (i) the requirement of a stoichiometric amount of PDC, which is fairly expensive for an industrial use, as a trapping agent for KNO_2 or K_2O, (ii) the requirement of a large excess of KF, because PDC consumes 2 equiv of KF to give PDF, and (iii) the feasibility of the explosion of the starting nitro compounds in fluorodenitrations.

We next attempted to use the fluorosulfonyl group as a leaving group replaced by fluoride ion. The so-called fluorodesulfonylations are known,[23] though their use in the synthesis of *m*-fluoro arenes, except for 1,3-benzenedisulfonyl derivatives, has barely been explored. Our research interest is in the development of general synthetic scheme for *m*-fluoro arenes by the use of fluorodesulfonylations.

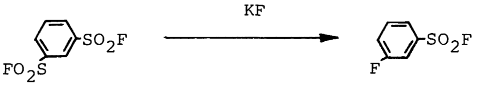
First of all, in order to evaluate the reported fluorodesulfonylation method, which could afford the desired 3-fluorobenzenesulfonyl fluoride (**5a**) in 45% yield, the reaction of 1,3-benzenedisulfonyl difluoride (**4a**)[26,27] with 2.2 equiv of KF in sulfolane at 240 °C was re-examined (Eq. 2). After 5 h, GLC analysis of

Table 4. Fluorodenitrations Catalyzed by Tetraphenylphosphonium Bromide[a]

Substrate		KF	Temp[b]	Time[b]	Product		Yield[c]	Bp/°C/mmHg or Mp/°C	Reported constant	Ref.
		equiv	°C	h			%			
	**1a**	4	180	3		**2a**	89	78—80/15	205/760	d)
	**1b**	4	210	2.5		**2b**	86	81—84/30	182.6/753	e)
	**1c**	5	180	2		**2c**	65	51—53	52-54	f)
	**1d**	6	210	8.5		**2d**	61	56—60/30	g)	h)
	**1e**	5	210	8		**2e**	57	78—82/20	78—80/20	i)
						**3e**	7[j]			
	**1f**	5	200	3		**2f**	56[k]	95—98/760	105/760	l)
	**1g**	4	210	8		**2g**	53[k]	100—103/760	101/760	m)
	**1h**	5	190	6		**2h**	46	80—85/15	76—80/11	n)
						**3h**	3[j]			
	**1i**	4	220	5.5		**2i**	27[j]		127.6/760	o)
						**2a**	16[j]		205/760	d)
	**1j**	5	220	8		**2j**	25	87—92/30	33—35	f)
	**1k**	4	210	5		**2k**	7[j]			
	**1l**	6	180	3		**2l**	0			

a) See experimental part. b) Reaction was performed at 150 °C for 2 h then at appropriate temperature. c) Isolated yield and all samples gave satisfactory IR, NMR, and mass spectra. d) E. D. Bergmann, S. Berkovic, and R. Ikan, *J. Am. Chem. Soc.*, **78**, 6037 (1956). e) Ref. 32. f) The Aldrich Fine Chemical Catalog Handbook, p. 539 (1988). g) This sample was identified as diethylamino derivative by comparison with the authentic sample which was prepared from 3-fluorobenzoyl chloride. Hydrolysis of **2d** gave 3-fluorobenzoic acid, mp 125 °C (mp 125 °C in Ref. h). h) J. Frederick, J. Dippy, and R. H. Lewis, *J. Chem. Soc.*, **1936**, 644. i) Ref. 23. j) Yield was determined by GLC. Compounds were identified by GC-MS. k) Use of reaction-distillation technique. l) W. J. Feast, W. K. R. Musgrave, and R. G. Weston, *J. Chem. Soc., C*, **1971**, 1547. m) L. V. Cherry, M. E. Hobbs, and H. A. Strobel, *J. Phys. Chem.*, **61**, 465 (1957). n) Ref. 20. o) H. S. Booth, H. M. Elsey, and P. E. Burchfield, *J. Am. Chem. Soc.*, **57**, 2064 (1935).

the reaction mixture revealed a complete disappearance of **4a**.



4a **5a** (2)

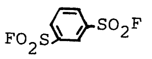
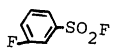
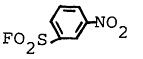
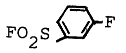
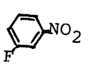
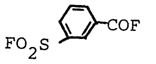
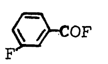
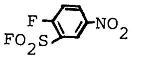
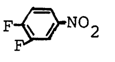
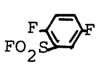
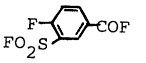
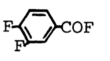
Direct distillation of the reaction mixture gave **5a** in 44% yield, which is very close to that reported.[23] With a sole isolated product, **5a**, a large amount of a tarry material was produced together. With the aim to improve the yield of **5a** along with a decrease of tarry materials, the use of Ph_4PBr and/or PDC was

Table 5. Reaction of 1,3-Benzenedisulfonyl Difluoride (**4a**) with Spray-Dried Potassium Fluoride under Various Conditions

Run	Temp	Time	KF	Ph_4PBr	Additive	Recovery of **4a**	Yield of **5a**
	°C	h	equiv	equiv	1 equiv	%	%
1	240	5	2.2	—	—	0	44
2	220	3	2.2	0.1	—	1	43
3	220	3	2.2	—	—	27	18
4	220	3	4.2	0.1	PDC	0	51, 49[a]
5	210	5	2.2	0.1	—	0	74[b]
6	240	5	2.2	—	—	0	57[b]

a) Duplicate experiment. b) Reaction-distillation technique.

Table 6. Fluorodesulfonylations by Use of Reaction-Distillation Technique[a]

Run	Substrate	Yield/%	Product
1	 **4a**	74	 **5a**
2	 **4b**	48	 **2e**  **3e** (7:1)
3	 **4c**	21[b]	 **2d**
4	 **4d**	49	 **2h**  **6d** (7:1)
5	**4d**	13[c]	**2h**+**6d**
6	 **4e**	45	 **5e**
7	**4e**	10[c]	**5e**

a) See experimental part. b) A 69% of **4c** was recovered. c) Without reaction-distillation technique.

attempted.

The use of 0.1 equiv of Ph_4PBr certainly accelerates the fluorination reaction, even though the yield of **5a** did not improve (Table 5, Run 2). Moreover, the addition of 1 equiv of PDC slightly effected an improvement in the reaction (Run 4). However, a more detailed examination did not take place because we judged that the method, which required a stoichiometric amount of PDC, did not have sufficient merit.

We hypothesized that reaction product **5a** might be unstable under the fluorination conditions at elevated temperature to give tarry materials. We confirmed this hypothesis by showing that use of a reaction-distillation technique to avoid any decomposition of the reaction product increased the yield of **5a**. Thus, the reaction of **4a** (50 mmol) and KF (110 mmol) in sulfolane (8.5 ml) in the presence of Ph_4PBr (5 mmol) at 210 °C under reduced pressure (270 mmHg)† for 5 h gave **5a** in 74% yield (Table 4, Run 5). Product **5a**, having a boiling point lower than that of sulfolane, was easily collected since it was distilled during the reaction. The distillate, **5a**, was almost in its pure form, including a small amount of sulfolane; washing with water, followed by distillation, gave pure **5a**. In the absence of Ph_4PBr, the use of reaction-distillation technique could also improve the yield of the desired **5a**, though a higher reaction temperature was required than that in the presence of Ph_4PBr.

Further evidence for the efficacy of the reaction-distillation technique in the improvement of the yields on fluorodesulfonylations catalyzed by Ph_4PBr is provided in Table 6; an application of the reported fluorodesulfonylation procedure to benzenesulfonyl fluoride derivatives carrying other functional group, such as NO_2 and COF, could not afford the desired *m*-fluoro arenes. For example, 3,4-difluorobenzoyl fluoride (**5e**) is an important synthetic intermediate for pharmaceutical products and agrochemicals. According to the reported procedure,[23] **5e** could be prepared

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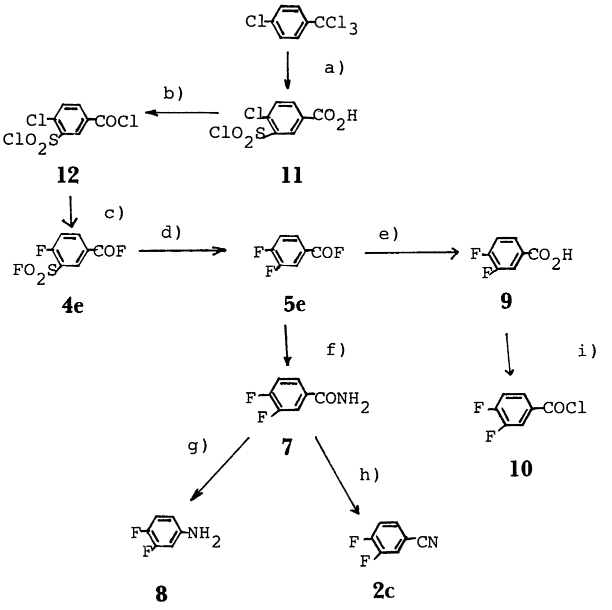
† 1 mmHg=133.32 Pa

from 4-fluoro-3-(fluorosulfonyl)benzoyl fluoride (**4e**) and KF. However, the yield was only 10% and a large amount of tarry materials was obtained (Table 6, Run 7). On the other hand, the present process (Ph_4PBr plus reaction-distillation) provided rapid progress concerning the aim to improve the yield of the desired products along with a decrease of tarry materials (Table 6, Run 6). However, the yield was still low, even after employing the explored method; continuing efforts will be necessary in order to realize industrial use.

Our **5e**, which is unknown in the literature, was identified as an acid form (**9**), mp 119—120 °C (lit,[28] mp 119.2—120 °C). 3,4-Difluoroaniline (**8**) and 3,4-difluorobenzonitrile (**2c**) readily derived from **5e** via 3,4-difluorobenzamide (**7**) are also useful intermediates.[28] They had been previously obtained from 3,4-difluorobenzoyl chloride (**10**), which was prepared from 1,2-difluorobenzene (DFB) or 3,4-difluorotoluene (DFT) in a multi-step synthesis.[28a] The fluorocarbons (DFB and DFT) have been prepared by employing a hazardous reagent, such as anhydrous hydrogen fluoride (HF), the handling of which requires caution.

As mentioned above, we have succeeded in developing a novel catalyzed reaction which is useful in the synthesis of *m*-fluoro aromatic derivatives. The catalytic reaction developed herein is anticipated to be one of the most practical and general synthetic methods of various structural types of *m*-fluoro arenes.



a) $ClSO_3H$, 150 °C, 2 h (100%). b) $SOCl_2$ in PhH, reflux, 8 h (94%). c) sd KF in CH_3CN, cat. Ph_4PBr, reflux, 24 h (71%). d) see text. e) 10% NaOH then 10% HCl (93%). f) 6% NH_4OH (82%). g) Br_2 in aq KOH, 0—88 °C, 1 h (65%). h) $SOCl_2$ in C_6H_5Cl, reflux, 3 h (71%). i) $SOCl_2$ in PhH, reflux (81%).

Scheme 3.

Experimental

General. All melting points were determined with a Yanaco micro melting point apparatus or Mettler FP61 melting point apparatus and were uncorrected. IR spectral measurements were carried out with a JASCO FT/IR-5M infrared spectrometer. NMR spectra were recorded with a JEOL model JNM-PMX 60 spectrometer. Mass spectra were taken with a Hewlett Packard model 5998A GC-Mass spectrometer using a 0.20 mm×25 m column of Ultra 2 (5% phenyl methyl silicone). Product mixtures were analyzed by GLC on a Shimadzu Model GC-7AG gas chromatograph using a 3 mm×2 m column of Dexsil 400GC on Chromosorb W AW DMCS. The temperature of the oil bath was controlled with the aid of a Ricoh Mini Heater Electric Controller, Model MH-10.

Unless stated otherwise, all reagents and chemicals were obtained commercially and used without further purification. Spray-dried potassium fluoride was purchased from Morita Kagaku Kogyo Co. or Reidel de Häen Co. Sulfolane was purchased from Seitetsu Kagaku Kogyo (Sumitomo Seika) Co. Tetraphenylphosphonium bromide was obtained from Hokko Kagaku Kogyo Co. or Tokyo Kasei Kogyo Co. 4-Chloro-3-nitrobenzonitrile was prepared according to the literature,[29] mp 98—101 °C (lit,[29] mp 101 °C). 2-Chloro-5-nitrobenzonitrile was prepared from 2-chlorobenzonitrile and mixed acid in 1,2-dichloroethane at 10—20 °C for 16 h, mp 103—107 °C (lit,[30] mp 106 °C). 2,4-Dichlorobenzonitrile was prepared according to a method described in the literature,[31] mp 56—60 °C (lit,[31] mp 61—62 °C), then usual nitration of the sample gave 2,4-dichloro-5-nitrobenzonitrile, mp 105—109 °C, which was identified by GC-MS.

General Procedure for Fluorodenitrations. Synthesis of 3-Fluorobenzonitrile (2b): A 100 ml four-necked flask equipped with a mechanical stirrer, a thermometer, and a water separator was charged with spray-dried KF (23.2 g, 0.4 mol), Ph_4PBr (4.2 g, 0.01 mol), sulfolane (50 g), and toluene (20 ml). The mixture was stirred in order to remove toluene azeotropically in an oil bath. After the flask was cooled to 120 °C, PDC (20.3 g 0.1 mol) and **1b** (14.8 g, 0.1 mol) were added in one portion. The whole mixture was stirred for 2 h at 150 °C and then for 2.5 h at 210 °C. The mixture was then cooled to room temperature and filtrated to remove inorganic materials. The residue was distilled to give pure **2b** (10.4 g, 84%) having a boiling point of 81—84 °C/30 mmHg (lit,[32] bp 182.6 °C/753 mmHg) and identical NMR, IR, and Mass spectra with those of an authentic sample.

General Procedure for Fluorodesulfonylations. a) Synthesis of 3-Fluorobenzenesulfonyl Fluoride (5a) (Table 5, Run 5): A 100 ml four-necked flask equipped with a mechanical stirrer, a thermometer, and a water separator was charged with spray-dried KF (6.5 g, 0.11 mol), Ph_4PBr (2.1 g, 5 mmol), sulfolane (8.5 ml), and toluene (20 ml). The mixture was stirred to remove toluene azeotropically. After the flask was cooled to 100 °C, the water separator was replaced by a distilling head and 1,3-benzenedisulfonyl difluoride (**4a**) (12.1 g, 0.05 mol) was added. The whole mixture was stirred at 210 °C under reduced pressure (270 mmHg) for 5 h. The product, having a boiling point (170 °C/270 mmHg) lower than that of sulfolane, was easily collected as it was distilled from the reaction mixture during the reaction. After washing with water, subsequent distillation resulted in pure **5a** (6.56 g, 74%), bp 87 °C/20 mmHg (lit,[23] bp 92—101 °C/20 mmHg).

b) Synthesis of 3,4-Difluoronitrobenzene (2h) (Table 6, Run 4): Treatments of 2-fluoro-5-nitrobenzenesulfonyl fluoride (**4d**) (11.15 g, 0.05 mol) with a mixture of spray-dried KF (6.5 g, 0.11 mol) and Ph_4PBr (2.1 g, 5 mmol) in sulfolane (8.5 ml) in a similar manner to that described in a) (210 °C, 300 mmHg), gave 7 : 1 mixture of **2h** and 2,5-difluorobenzenesulfonyl fluoride (**6d**) (3.88 g), bp 86—88 °C/20 mmHg, which could not be separated (lit,[20] bp 76—80 °C/11 mmHg as for **2h**). GC-MS: m/z 159 (M^+ for **2h**) and 196 (M^+ for **6d**).

c) Synthesis of 3,4-Difluorobenzoyl Fluoride (5e) (Table 6, Run 6): Treatments of 3-fluorosulfonyl-4-fluorobenzoyl fluoride (**4e**) (11.2 g, 0.05 mol) with a mixture of spray-dried KF (6.5 g, 0.11 mol), and Ph_4PBr (2.1 g, 5 mmol) in sulfolane (8.5 ml) at 210 °C and 270 mmHg in the same manner to that described in a), followed by washing with water and purification by redistillation (bp 74 °C/75 mmHg), gave **5e** (3.21 g, 45%). GC-MS: m/z 160 (M^+). Found: m/z 160.0135, Calcd for $C_7H_3F_3O$: m/z 160.0136. IR (neat): 1820 cm^{-1}.

Hydrolysis of 5e into 3,4-Difluorobenzoic Acid (9). Compound **5e** (1.0 g, 6.25 mmol) was treated in 10% NaOH (10 ml) for 1 h, followed by neutralization with 15% HCl to pH 6—7. The precipitated **9** was collected by filtration, washed with water, and recrystallized from hexane. Yield 0.93 g (93%). Mp 119—120 °C (lit,[28a)] mp 119.2—120.1 °C). The IR spectrum of this sample was identical with that of authentic **9**.

3,4-Difluorobenzamide (7). To a mixture of 25% aqueous ammonia (9.8 g) and water (5.6 g) was added dropwise **5e** (4.5 g, 28 mmol) with stirring. After being stirred for 2 h, filtration and concentration of the reaction mixture afforded 3.6 g (82%) of **7**, mp 129—130 °C. IR (KBr): 3380, 3180, and 1660 cm^{-1}. MS: m/z 157 (M^+). Found: C, 53.18, H; 3.39, N; 8.59%, Calcd for $C_7H_5NF_2O$: C; 53.51, H; 3.21, N; 8.91%.

3,4-Difluoroaniline (8). Compound **7** (7.85 g, 50 mmol) was added to a mixture of KOH (14.0 g, 250 mmol), bromine (8.0 g, 50 mmol) and water (80 ml) at 0 °C. The mixture was gradually heated to 88 °C for 1 h. After cooling, the resulting mixture was poured into a water, then extracted with ether. After being dried over Na_2SO_4, filtration and concentration in vacuo gave a residue, which was distilled to give 4.2 g (65%) of **8** having a bp 92 °C/20 mmHg (lit,[33] bp 77 °C/7 mmHg). The IR and MS spectra were identical with those of authentic **8**.

3,4-Difluorobenzonitrile (2c). A mixture of **7** (7.85 g, 50 mmol) and thionyl chloride (12.0 g, 100 mmol) in chlorobenzene (25 g) was heated at reflux for 3 h. After removal of excess thionyl chloride and chlorobenzene, the residue was distilled to give **2c** (4.9 g, 71%) having bp 77 °C/20 mmHg and mp 51.0—51.2 °C (lit,[1] mp 51—53 °C). IR(KBr): 2340 cm^{-1}. MS: m/z 139 (M^+).

4-Chloro-3-(chlorosulfonyl)benzoic Acid (11). Chlorosulfuric acid (290 g, 2.5 mol) was added to 1-chloro-4-(trichloromethyl)benzene (115 g, 0.5 mol) with stirring. The mixture was heated at 120 °C for 1 h then at 150 °C for 2 h. After cooling, the resulting liquid was added in small portions onto ice, then extracted with ether. The ether extract was washed with water, dried, and concentrated in vacuo to give a crude **11** (127.9 g, 100%), which was used without purification in the next step.

4-Fluoro-3-(fluorosulfonyl)benzoyl Fluoride (4e). Thionyl chloride (357 g, 3 mol) was added dropwise under stirring to a refluxing mixture of **11** (255 g, 1 mol) and benzene (0.5 l); the reflux was continued for 7 h. After removal of benzene and excess of thionyl chloride, the residue was distilled under reduced pressure (bp 151 °C/1 mmHg) to afford pure 4-chloro-3-(chlorosulfonyl)benzoyl chloride (**12**) (257 g, 94%). A mixture of **12** (27.3 g, 0.1 mol), spray-dried KF (23.2 g, 0.4 mol), Ph_4PBr (4.2 g, 0.01 mol) in anhydrous acetonitrile (100 ml) was refluxed for 16 h. Filtration and concentration, followed by distillation, gave 16 g (71%) of **4e** having a bp 85 °C/1 mmHg. IR (neat): 1830 and 1220 cm^{-1}. Found: m/z 223.9739, Calcd for $C_7H_3F_3SO_3$: m/z 223.9754.

1-Fluoro-2-fluorosulfonyl-4-nitrobenzene (4d). To a molten 1-chloro-4-nitrobenzene (15.75 g, 0.10 mol) was added 30% fuming sulfuric acid (29.3 g, 0.11 mol) at 83 °C. The whole mixture was stirred at 110—115 °C for 16 h. The resulting mixture was carefully poured into 80 ml of water while stirring well. Then, 48% NaOH was added in order to precipitate the sodium salt of the sulfonic acid, which was collected by filtration, washed with water, and dried. Yield 23.66 g (100%). To a mixture of sodium 2-chloro-5-nitrobenzenesulfonate (18.17 g, 0.070 mol), acetonitrile (35 ml), sulfolane (35 ml), and *N,N*-dimethylacetamide (1.75 ml) was added phosphoryl chloride (42.9 g, 0.28 mol) at 70 °C. After an additional hour's reaction, the resulting mixture was poured into water, and extracted with ether. The ether layer was washed with water, dried, and concentrated to afford 14.4 g (80%) of 1-chloro-2-chlorosulfonyl-4-nitrobenzene. A mixture of Ph_4PBr (6.7 g, 16 mmol), spray-dried KF (46.5 g, 0.80 mol), and sulfolane (192 g) was dehydrated with toluene azeotropically. To the mixture was added 1-chloro-2-chlorosulfonyl-4-nitrobenzene (84.5 g, 0.32 mol) in one portion. The whole mixture was heated at 130—140 °C for 16 h. After filtration to remove inorganic matter, ether (0.5 l) and water (0.3 l) were added. The organic layer was separated, washed with water, and dried over Na_2SO_4. Filtration and concentration in vacuo gave a residue, which was distilled to afford 64.8 g (90%) of **4d** having a bp 115 °C/0.3 mmHg. IR (neat): 1620, 1595, 1545, 1490, 1430, 1360, 1270, 1225, 1075, 910, 805 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ=7.4—7.9 (m, 1H), 8.5—9.0 (m, 2H). MS: m/z 223 (M^+).

1,3-Benzenedisulfonyl Difluoride (4a). To a mixture of disodium 1,3-benzenedisulfonate (56.44 g, 0.2 mol), acetonitrile (100 ml), sulfolane (100 ml), and *N,N*-dimethylacetamide (5 ml) was added phosphoryl chloride (245.3 g, 1.6 mol) at 70 °C during for 1 h. After an additional 3 h reaction, the resulting mixture was poured into water (300 ml), and extracted with ether (500 ml). The etherate was washed with water, dried, and concentrated to give 46.2 g (84%) of crude 1,3-benzenedisulfonyl dichloride. A mixture of 1,3-benzenedisulfonyl dichloride (46.2 g, 0.17 mol) prepared as mentioned above, KF (39.0 g, 0.67 mol), and Ph_4PBr (7.04 g, 17 mmol) in anhydrous acetonitrile (170 ml) was heated at reflux for 16 h. Filtration and concentration, followed by distillation, gave pure **4a** (35.3 g, 87%) having a bp 112 °C/1 mmHg (lit,[23] bp 98—104 °C/0.5 mmHg). IR (neat): 1580, 1410, 1300, 1220, 1120, 1080, 820, 780, 750 cm^{-1}. MS: m/z 242 (M^+).

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