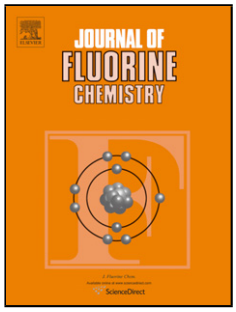

Title: Dibromofluoromethylation of aryl Grignard reagents with dibromodifluoromethane in the presence of LiBr

Author: Masahiro Shiosaki Munenori Inoue

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Highlights

- The dibromofluoromethylation of aryl Grignard reagents was developed.
- The reaction proceeded *via* a difluorocarbene-mediated mechanism.
- α,α-Dibromo-α-fluorotoluene derivatives were obtained.

Graphical Abstract

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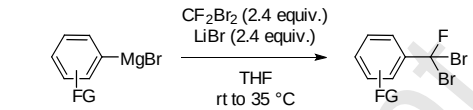

Masahiro Shiosaki [a,b], Munenori Inoue [a,*]

[a] *Sagami Chemical Research Institute (SCRI), 2743-1 Hayakawa, Ayase, Kanagawa 252-1193, Japan*

[b] *Department of Electronic Chemistry, Tokyo Institute of Technology, Nagatsuta, Midori-Ku, Yokohama 226-8502, Japan*

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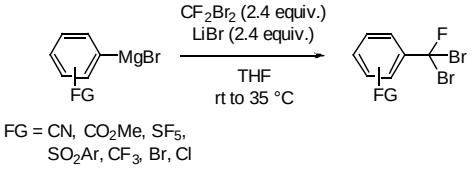


Dibromofluoromethylation of aryl Grignard reagents with dibromodifluoromethane in the presence of LiBr

Masahiro Shiosaki [a,b], Munenori Inoue [a,*]

[a] *Sagami Chemical Research Institute (SCRI), 2743-1 Hayakawa, Ayase, Kanagawa 252-1193, Japan*

[b] *Department of Electronic Chemistry, Tokyo Institute of Technology, Nagatsuta, Midori-Ku, Yokohama 226-8502, Japan*

** Corresponding author. Tel.: +81 467−77−4208; fax: +81 467−77−4113.*

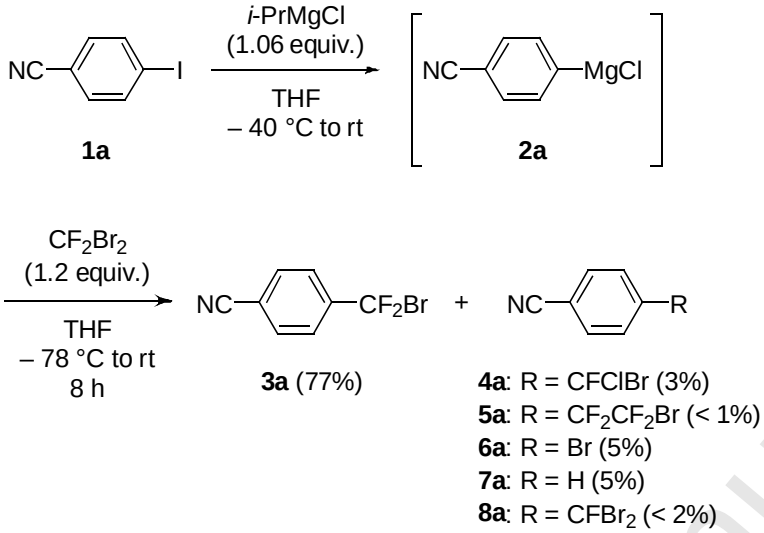
E-mail address: inoue@sagami.or.jp (M. Inoue).

Abstract—The dibromofluoromethylation of aryl Grignard reagents bearing electron-withdrawing groups with dibromodifluoromethane (CF_2Br_2) proceeded in the presence of LiBr. The reaction gave the corresponding α,α-dibromo-α-fluorotoluene derivatives through halogen exchange reaction of intermediate difluorobenzyl anions.

Keywords: Dibromofluoromethylation, Aromatic Grignard reagents, Difluorocarbene, Organofluorine compounds

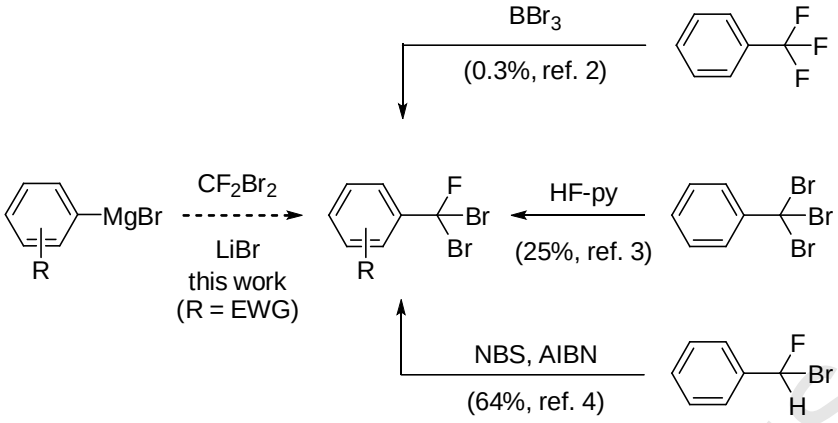
1. Introduction

In the previous paper, we reported that the bromodifluoromethylation of aromatic Grignard reagents possessing electron-withdrawing groups with dibromodifluoromethane (CF_2Br_2) at −78 °C afforded the corresponding α-bromo-α,α-difluorotoluene derivatives [1]. In the reaction between 4-cyanophenylmagnesium chloride (**2a**) and CF_2Br_2, a 77% GC yield of α-bromo-α,α-difluorotoluene **3a** was produced along with several side products including α-bromo-α-chloro-α-fluorotoluene **4a** and bromide **6a** as shown in Scheme 1. After publishing the paper, we carefully reinvestigated the side products and realized that α,α-dibromo-α-fluorotoluene **8a** was also formed in less than 2% yield by GC analysis.



Scheme 1. Bromodifluoromethylation of 4-cyanophenylmagnesium chloride (**2a**) [1].

α,α-Dibromo-α-fluorotoluene derivatives are a little-known class of organofluorine compounds and only the following synthetic examples have been disclosed so far. Prakash et al reported that halogen-exchange reaction of α,α,α-trifluorotoluene with BBr_3 produced a 43% yield of α-bromo-α,α-difluorotoluene as the major product with the formation of a trace amount (0.3%) of α,α-dibromo-α-fluorotoluene as depicted in Scheme 2 [2]. As an alternative method, the bromine-fluorine exchange reaction of α,α,α-tribromotoluene with HF-pyridine was disclosed by Cai et al [3], where α,α-dibromo-α-fluorotoluene was obtained in 25% yield. Furthermore, α,α-dibromo-α-fluorotoluene was prepared from α-bromo-α-fluorotoluene in 64% through radical bromination using *N*-bromosuccinimide and AIBN by Kusei et al, who used it as a precursor of fluorophenylcarbene [4].



Scheme 2. Formation of α,α-dibromo-α-fluorotoluene derivatives.

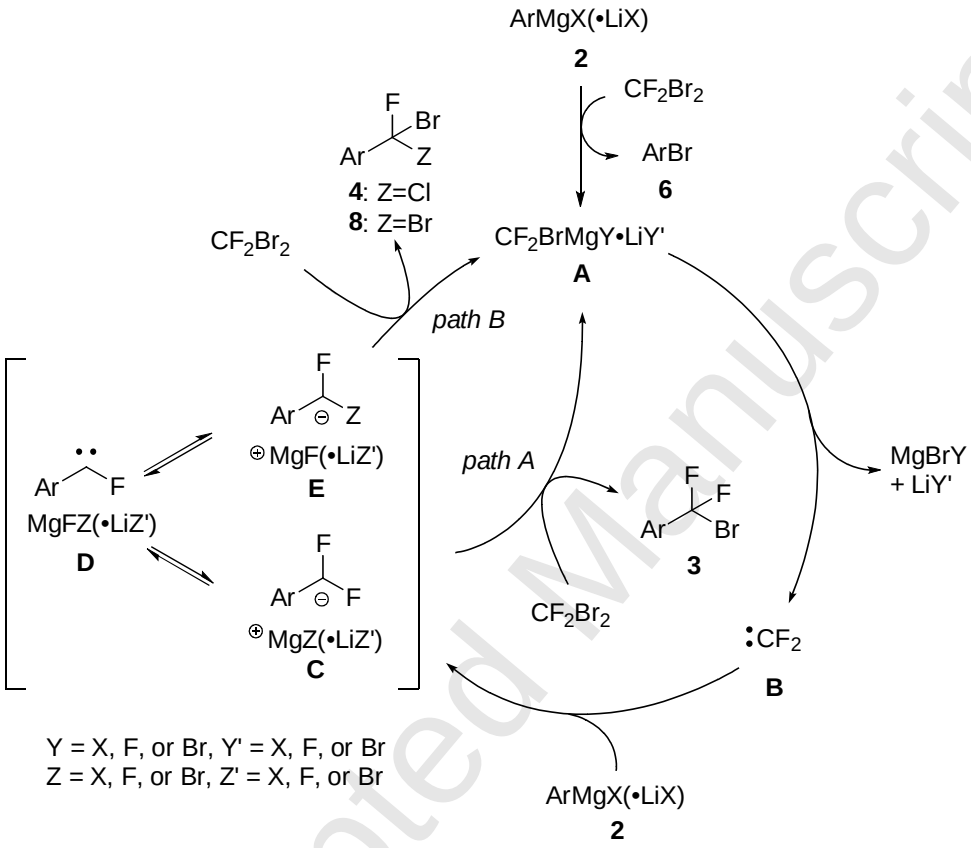
Since organofluorine compounds are of great importance in the areas of pharmaceutical, agrochemical and material sciences [5], we envisaged α,α-dibromo-α-fluorotoluene derivatives would also potentially serve as biologically active molecules [6]. In addition, they could be transformed into other important fluorinated compounds by nucleophilic substitution reactions of the dibromofluoromethyl ($CFBr_2$) group. Several transformations of the $CFBr_2$ group, such as 1,2-difluroalkene synthesis [7], Reformatsky reaction [8] and aldol reaction [9] of dibromofluoroacetic acid derivatives [10], azide substitution [11], manganation [12], magnesiation [13], and zincation [14], have been reported, however, in terms of α,α-dibromo-α-fluorotoluene derivatives, their reactivity is not studied at all except for Kusei's work [4]. The reported methods of synthesizing α,α-dibromo-α-fluorotoluene derivatives as mentioned in Scheme 2 required harsh reaction conditions and inaccessible starting materials, and had limited substrate scope. Therefore, as an extension of our previous research, we initiated to study the reaction conditions to obtain α,α-dibromo-α-fluorotoluene derivatives as major products and explore the

reactivity of these compounds. Herein, we would like to present the dibromofluoromethylation of aromatic Grignard reagents with CF_2Br_2 in the presence of LiBr (Scheme 2).

2. Results and discussion

As well as other bromodifluoromethylations using CF_2Br_2 as a source of the bromodifluoromethyl group [15], we speculated that our developed aromatic bromodifluoromethylation (Scheme 1) proceeded via a difluorocarbene-mediated mechanism as shown in Scheme 3. The reaction initiated by bromination of aryl Grignard reagent (**2**, X=Cl) with CF_2Br_2 to produce aryl bromide **6** and bromodifluoromethyl anion **A**, which was immediately decomposed to difluorocarbene **B**. The key intermediate in this reaction was difluorobenzyl anion **C** derived from aryl Grignard reagent **2** and difluorocarbene **B**. When the reaction was carried out at −78 °C in the absence of LiCl (= LiX) as an additive, the major product was bromodifluoromethyl compound **3**, which indicated that bromination of **C** (path A) predominantly took place. As side products, bromochlorofluoromethyl compound **4** and dibromofluoromethyl compound **8** were formed in less than 3% yield, respectively, by a halogen exchange reaction via arylfluorocarbene **D** (**C** −> **D** −> **E**) [16], followed by bromination of **E** (path B). The suppression of these undesired side reactions may be due to the slow α-elimination (**C** −> **D**) rate at −78 °C [17]. Therefore, from the viewpoint of the reaction mechanism, the acceleration of the halogen exchange reaction (**C** −> **E**) should be the key to success for obtaining dibromofluoromethyl compound **8** as a major product. We envisioned that undertaking the reaction at ambient temperature to accelerate the α-elimination and increasing the concentration of bromide ion by using

Ar-MgBr as **2** and the addition of lithium bromide to the reaction media would improve the yield of **8**.



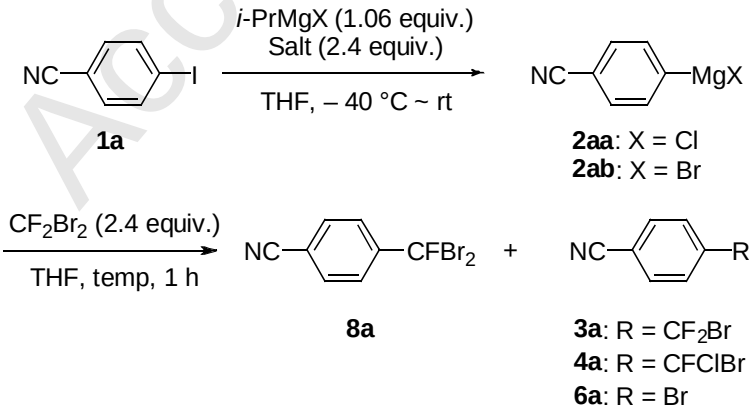
Scheme 3. Plausible reaction mechanism of aromatic trihalomethylations.

Initially, we investigated the reaction between 4-cyanophenylmagnesium reagent and CF_2Br_2 in the presence of LiBr at ambient temperature as shown in Table 1. Exposure of ArMgCl **2aa**, prepared from 4-iodobenzonitrile **1a** and *i*-PrMgCl in the presence of LiBr [18], to a solution of 2.4 equiv. of CF_2Br_2 in THF at room temperature produced a 23% GC yield of the targeted compound **8a** (entry 3). Compared to the previously reported conditions (entries 1 and 2), in which the reaction was carried out at −78 °C, the yield of **8a** was increased and formation of **3a** was dramatically suppressed

as expected. Unfortunately, the yield of bromochlorofluoromethyl compound **4a** was also increased to 18%. Next, *i*-PrMgBr was used for the magnesiation of **1a** to eliminate the chlorine atom source of **4a** (entry 4). The reaction afforded a 41% GC yield of **8a** without formation of **4a**. Since the yield of **8a** was decreased in the absence of LiBr (entry 5), the addition of LiBr is effective. Furthermore, we carried out the reaction at between room temperature to 35 °C, giving rise to an improved yield of the product (49% GC yield, entry 6). The yield of the desired product was decreased when the reaction was performed at 60 °C (entry 7). Using an excess amount of CF_2Br_2 (4.8 equiv.) in the reaction was not effective (entry 8). Next, we evaluated the effect of other bromide salts, such as NaBr, KBr, and tetra-*n*-butylammonium bromide (TBAB) (entries 9−11), however, the yield was not improved. The reaction conditions in entry 6 gave the best result and the desired product **8a** was isolated in 43% yield after purification by silica gel column chromatography and recycle GPC to remove the side products.

Table 1

Dibromofluoromethylation of aryl Grignard reagent **2**.[a]



Entry	X	Salt	Temperature	GC yield (%)[b]

				8a	**3a**	**4a**	**6a**
1[c]	Cl	LiCl	−78 °C	3	50	7	13
2[c]	Cl	None	−78 °C	2	77	3	5
3	Cl	LiBr	rt	23	2	18	1
4	Br	LiBr	rt	41	5	0	4
5	Br	None	rt	32	19	0	5
6	Br	LiBr	rt ~ 35 °C	49 (43)[d]	2	0	4
7	Br	LiBr	60 °C	32	11	0	2
8[e]	Br	LiBr	rt ~ 35 °C	40	2	0	4
9	Br	NaBr	rt ~ 35 °C	21	16	0	6
10	Br	KBr	rt ~ 35 °C	29	17	0	7
11[f]	Br	TBAB	rt ~ 35 °C	13	7	0	4

[a] The Grignard reagent was added dropwise into a solution of CF_2Br_2 in THF.

[b] Determined by GC analysis using undecane as an internal standard.

[c] See ref. 1. The yield of **8a** was obtained after its publication.

[d] Isolated yield.

[e] 4.8 equiv. of CF_2Br_2 were used.

[f] 1.2 equiv. of tetrabutylammonium bromide (TBAB) were used.

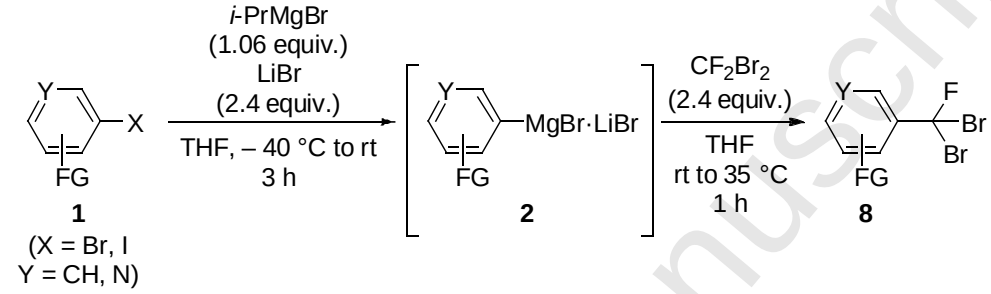
With the optimized conditions, the substrate scope of this dibromofluoromethylation was evaluated by using several aryl Grignard reagents **2** bearing electron-withdrawing groups as shown in Table 2. The dibromofluoromethylation of *m*- and *o*-cyanophenyl Grignard reagents with CF_2Br_2 gave the corresponding products in 25 and 37% isolated yields, respectively. Since the yield of the *m*-cyano substituted substrate was slightly reduced compared with those of the *o*- and *p*-isomers, the *o*- and *p*-cyano groups stabilized the intermediate anions **C** and **E** and this resonance effect facilitated the reaction. In the case of the *o*- and *p*-cyanophenyl Grignard reagents substituted by electron donating groups, such as methyl and methoxy groups, the desired products **8d**~**8g** were obtained in 12~32% yields. Interestingly, in the reaction with 4-cyano-3-fluorophenylmagnesium bromide, the desired dibromofluoromethyl

compound **8h** was not afforded and the corresponding bromodifluoromethyl compound was mainly produced. We regarded that the inductive effect of the fluorine atom along with the resonance effect of the cyano group stabilized the intermediate **C** and delayed the halogen exchange reaction. Next, we examined aromatic Grignard reagents possessing other electron-withdrawing groups. 4-(Methoxycarbonyl)phenylmagnesium bromide and 4-(pentafluorosulfanyl)phenylmagnesium bromide were allowed to react with CF_2Br_2 in the presence of LiBr, affording **8i** and **8j** in around 30% yields. In addition, the reaction of (arylsulfonyl)phenylmagnesium bromides proceeded with the formation of **8k** and **8l** in moderate yields. From 2-bromo-1,3-dichloro-5-iodobenzene, the regioselective dibromofluoromethylation occurred to produce **8m**. While the yield was diminished to 6%, 4-(trifluoromethyl)phenylmagnesium iodide gave **8n**. This reaction was also applicable to a pyridyl Grignard reagent to obtain **8o**. Unfortunately, phenylmagnesium bromide and 4-methoxyphenylmagnesium bromide did not offer the desired products (**8p** and **8q**, respectively) at all. At the moment, this reaction is limited to aromatic Grignard reagents possessing electron-withdrawing groups. In the reported bromodifluoromethylation of aromatic Grignard reagents with CF_2Br_2 [1], the yield of the reaction was dependent on the substituent on the aromatic ring and the preferred order is –CN > $-SO_2Ph$ > $-CO_2R$ > $-CF_3$. In this dibromofluoromethylation, the order is the same. With decreasing the yield of the desired dibromofluoromethylated product, the formation of the brominated product, the protonated product, and unidentified products detected by GC and NMR was increased. A plausible mechanism of this reaction is postulated as shown in Scheme 3 (X = Z = Br). As expected, the reaction temperature (at between room temperature and 35 °C) and the increasing concentration

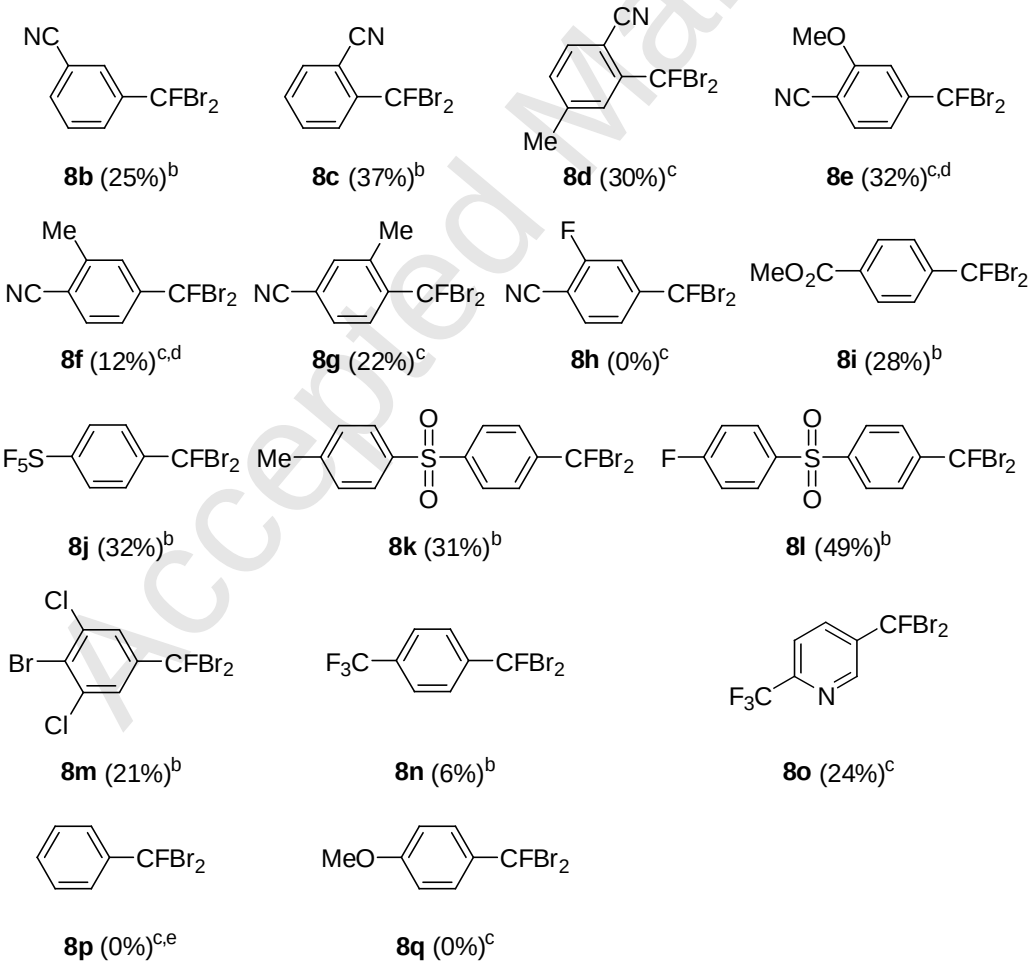
of bromide ion are keys to accelerate the fluorine-bromine exchange reaction (**C** to **E**) and progress the desired reaction.

Table 2

Scope of the dibromofluoromethylation of several (hetero)aryl Grignard reagents.[a]



1 (X = Br, I; Y = CH, N) **2** **8**



8b (25%)[b] **8c** (37%)[b] **8d** (30%)[c] **8e** (32%)[c,d]

8f (12%)[c,d] **8g** (22%)[c] **8h** (0%)[c] **8i** (28%)[b]

8j (32%)[b] **8k** (31%)[b] **8l** (49%)[b]

8m (21%)[b] **8n** (6%)[b] **8o** (24%)[c]

8p (0%)[c,e] **8q** (0%)[c]

[a] Isolated yield.

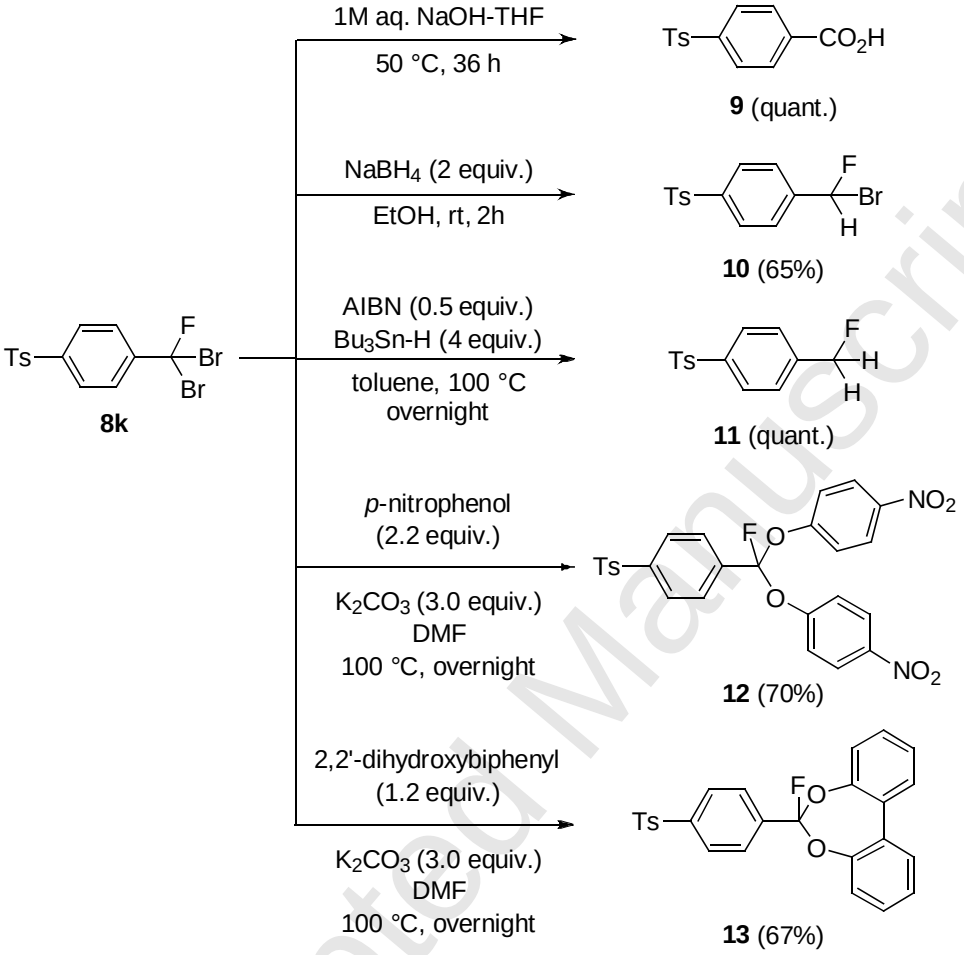
[b] Aryl iodide **1** was used for the reaction.

[c] Aryl bromide **1** was used for the reaction.

[d] 2.12 equiv. of *i*-PrMgBr were used.

[e] Mg (1.2 equiv.) was used instead of *i*-PrMgBr.

Finally, we surveyed the reactivity of α,α-dibromo-α-fluorotoluene derivatives as depicted in Scheme 4. At the beginning, we evaluated the stability of these compounds under acidic and basic conditions. Subjection of dibromofluoromethyl compound **8k** to a mixture 1M aq. HCl-THF at 50 °C for 36 hrs resulted in no decomposition of **8k**, which was quantitatively recovered. In contrast, gradual degradation of **8k** to the corresponding carboxylic acid **9** [19] was observed under basic condition (1M aq. NaOH-THF at 50 °C). Next, we examined reduction of **8k** with $NaBH_4$ in EtOH, producing α-bromo-α-fluorotoluene derivative **10** in 65% yield. Complete reduction of **8k** to α-fluorotoluene **11** was achieved under radical reaction conditions (AIBN and *n*-Bu_3SnH). The nucleophilic substitution reaction of **8k** with 4-nitorophenoxide afforded a 70% yield of diphenylacetal **12**. While this method was not applicable to the reaction of catechol, cyclic acetal **13** [20] was obtained in 67% yield by heating of **8k** in the presence of 2,2'-dihydroxybiphenyl and K_2CO_3.



Scheme 4. Derivatization of **8k**.

3. Conclusion

In this paper, we described the novel dibromofluoromethylation of aryl Grignard reagents having electron-withdrawing groups with CF_2Br_2 in the presence of LiBr at between room temperature and 35 °C, producing α,α-dibromo-α-fluorotoluene derivatives. Several substrates with electron-withdrawing groups including –CN, $–CO_2Me$, $–SF_5$, $–SO_2Ar$, $–CF_3$, and halides, were applicable to this reaction. Although the resulting products were stable under acidic condition, they were hydrolyzed to the

carboxylic acids under basic condition. In addition, the dibromofluoromethyl group was successfully converted to the corresponding bromofluoromethyl, fluoromethyl, and bis(aryloxy)fluoromethyl groups by nucleophilic substitution reactions.

4. Experimental

4.1. General

All reactions involving air- and moisture–sensitive reagents were carried out using oven-dried glassware and standard syringe-septum cap techniques. Routine monitoring of reaction was carried out using glass-supported Merck silica gel 60 F_{254}TLC plates. Flash column chromatography was performed on Kanto chemical Silica Gel 60 N (spherical, neutral 40–50 μm). Recycle GPC was conducted using $CHCl_3$ as eluent on a JAI LC-9104. All solvents and reagents were obtained from commercial supplier and were used without further purification. Infrared (IR) spectral measurements were carried out with a HORIBA FT-720 spectrometer. ^{1}H, ^{13}C, and ^{19}F NMR spectra were measured with a Bruker AVANCE III spectrometer. Chemical shifts are expressed in parts per million (ppm) using tetramethylsilane (δ= 0, ^{1}H NMR and ^{13}C NMR) and C_6F_6 (δ = –163.0, ^{19}F NMR) as standard substances. Multiplicities are indicated by s (singlet), d (doublet), t (triplet), qui (quintet), dd (doublet of doublet), td (triplet of doublet), ddd (double of doublet of doublet), and m (multiplet). Melting points were taken on Mettler Toledo MP70 melting point system and uncorrected. Low-resolution mass (MS) spectra were measured on a Shimadzu GCMS-QP2010. High-resolution mass (HRMS) spectra were measured on a JEOL MStation JMS-700 mass spectrometer.

4.2. General procedure for the dibromofluoromethylation of aryl Grignard reagent ***2****, prepared from aryl halide (Ar-X,* ***1****) and i-PrMgBr, with CF_2Br_2 in the presence of LiBr.*

To a stirred mixture of Ar-X (**1**, 1.0 mmol) and lithium bromide (208 mg, 2.4 mmol) in THF (3.5 mL) was added dropwise a solution of *i*-PrMgBr in THF (2.0 M, 0.53 mL, 1.06 mmol) at –40 °C under Ar and the resulting mixture was stirred at –40 °C for 10 min and at room temperature for 3 h. To a stirred solution of dibromodifluoromethane (CF_2Br_2) in THF (4.90 M, 0.49 mL, 2.4 mmol) was added dropwise the prepared solution of ArMgBr **2** in THF via cannula at between room temperature and 35 °C over 1 min. and the resulting solution was stirred for 1 h. The reaction was quenched with saturated aqueous NH_4Cl (10 mL) and extracted with EtOAc (10 mL x 3). The combined extracts were dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by silica gel column chromatography (hexane/EtOAc = 10/1) and recycle GPC to give α,α-dibromo-α-fluorotoluene derivative **8**.

*4.2.1. 4-(Dibromofluoromethyl)benzonitrile (****8a****).* The reaction was carried out according to the general procedure using 4-iodobenzonitrile as Ar-X. White solid (124.1 mg, 43%). mp: 86.9–88.4 °C. IR (neat): 2235, 1406, 1270, 1230, 1047, 1016, 872, 752, 696 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, J = 8.6 Hz, 2H), 7.73 (d, J = 8.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.3 (d, J = 21.0 Hz, 1C), 132.3 (s, 2C), 124.9 (d, J = 7.1 Hz, 2C), 117.6 (s, 1C), 114.5 (s, 1C), 88.4 (d, J = 314.8 Hz, 1C). ^{19}F NMR (376 MHz, $CDCl_3$): δ –58.0 (s, 1F). GCMS-EI: *m/z* 214 $[M+2–Br]^+$ (97.7), 212 $[M–Br]^+$ (100), 133 $[M–2Br]^+$ (41.3), 102 $[M–CBr_2F]^+$ (1.0). HRMS-EI: *m/z* $[M]^+$ Calcd for $C_8H_4Br_2FN$: 290.8695 ; found: 290.8702.

*4.2.2. 3-(Dibromofluoromethyl)benzonitrile (**8b**).* The reaction was carried out according to the general procedure using 3-iodobenzonitrile as Ar–X. White solid (73.6 mg, 25%). mp. 46.3–47.8 °C. IR (neat): 2235, 1479, 1423, 1323, 1250, 1147, 1103, 941, 926, 742, 681, 656 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (dd, J = 1.1, 1.3 Hz, 1H), 7.90 (ddd, J = 1.1, 1.3, 8.0 Hz, 1H), 7.70 (ddd, J = 1.3, 1.3, 7.8 Hz, 1H), 7.58 (dd, J = 7.8, 8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.8 (d, J = 21.3 Hz, 1C), 133.9 (s, 1C), 129.6 (s, 1C), 128.4 (d, J = 6.6 Hz, 1C), 127.7 (d, J = 7.4 Hz, 1C), 117.5 (s, 1C), 113.0 (s, 1C), 88.0 (d, J = 314.3 Hz, 1C). ^{19}F NMR (376 MHz, $CDCl_3$): δ –57.7 (s, 1F). GCMS-EI: *m/z* 214 $[M+2–Br]^+$ (98.4), 212 $[M–Br]^+$ (100), 133 $[M–2Br]^+$ (42.6), 102 $[M–CBr_2F]^+$ (1.1). HRMS-EI: *m/z* $[M]^+$ Calcd for $C_8H_4Br_2FN$: 290.8695; found: 290.8695.

*4.2.3. 2-(Dibromofluoromethyl)benzonitrile (**8c**).* The reaction was carried out according to the general procedure using 2-iodobenzonitrile as Ar–X. White solid (107.7 mg, 37%). mp. 87.9–91.2 °C. IR (neat): 2227, 1487, 1442, 1288, 1259, 1225, 1144, 1117, 1036, 893, 866, 754, 694, 667, 631 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (d, J = 7.6 Hz, 1H), 7.80 (d, J = 7.6 Hz, 1H), 7.65 (t, J = 7.6 Hz, 1H), 7.58 (t, J = 7.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.8 (d, J = 20.7 Hz, 1C), 135.5 (s, 1C), 132.5 (d, J = 1.6 Hz, 1C), 130.7 (s, 1C), 124.2 (d, J = 11.0 Hz, 1C), 116.0 (s, 1C), 109.4 (d, J = 3.1 Hz, 1C), 86.1 (d, J = 313.9 Hz, 1C). ^{19}F NMR (376 MHz, $CDCl_3$): δ –55.5 (s, 1F). GCMS-EI: *m/z* 214 $[M+2–Br]^+$ (97.3), 212 $[M–Br]^+$ (100), 133 $[M–2Br]^+$ (39.1), 102 $[M–CBr_2F]^+$ (0.7). HRMS-EI: *m/z* $[M]^+$ Calcd for $C_8H_4Br_2FN$: 290.8695; found: 290.8695.

*4.2.4. 2-(Dibromofluoromethyl)-4-methylbenzonitrile (**8d**)*. The reaction was carried out according to the general procedure using 2-bromo-4-methylbenzonitrile as Ar–X. White solid (78.8 mg, 30%). mp. 134.6–136.2 °C. IR (neat): 2360, 2225, 1601, 1495, 1286, 1244, 1163, 1132, 1053, 953, 827, 818, 789, 762, 702, 644 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (d, J = 7.9 Hz, 1H), 7.58 (s, 1H), 7.31 (d, J = 7.9 Hz, 1H), 2.48 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.6 (d, J = 20.3 Hz, 1C), 143.9 (s, 1C), 135.4 (s, 1C), 131.3 (s, 1C), 124.9 (d, J = 10.9 Hz, 1C), 116.3 (s, 1C), 106.3 (d, J = 3.2 Hz, 1C), 86.3 (d, J = 314.0 Hz, 1C), 22.0 (s, 1C). ^{19}F NMR (376 MHz, $CDCl_3$): δ –55.3 (s, 1F). GCMS-EI: *m/z* 228 $[M+2–Br]^+$ (99.2), 226 $[M–Br]^+$ (100), 147 $[M–2Br]^+$ (14.2), 116 $[M–CBr_2F]^+$ (0.5). HRMS-EI: *m/z* $[M]^+$ Calcd for $C_9H_6Br_2FN$: 304.8851; found: 304.8854.

*4.2.5. 4-(Dibromofluoromethyl)-2-methoxybenzonitrile (**8e**)*. The reaction was carried out according to the general procedure using 4-bromo-2-methoxybenzonitrile as Ar–X except for using 2.12 equiv. of *i*-PrMgBr. Yellow solid (103.8 mg, 32%). mp. 72.2–74.3 °C. IR (neat): 2227, 1604, 1572, 1500, 1464, 1408, 1286, 1273, 1225, 1198, 1169, 1113, 1057, 1018, 933, 839, 796, 748, 719 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63 (d, J = 8.2 Hz, 1H), 7.32 (dd, J = 1.7, 8.2 Hz, 1H), 7.21 (d, J = 1.7 Hz, 1H), 4.01 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.9 (s, 1C), 149.9 (d, J = 20.9 Hz, 1C), 133.9 (s, 1C), 116.7 (d, J = 7.2 Hz, 1C), 115.2 (s, 1C), 107.0 (d, J = 7.9 Hz, 1C), 103.8 (s, 1C), 88.4 (d, J = 314.9 Hz, 1C), 56.4 (s, 1C). ^{19}F NMR (376 MHz, $CDCl_3$): δ –57.4 (s, 1F). GCMS-EI: *m/z* 325 $[M+4]^+$ (2.1), 323 $[M+2]^+$ (4.2), 321 $[M]^+$ (2.2), 244 $[M+2–Br]^+$

(99.0), 242 $[M–Br]^+$ (100). HRMS-EI: *m/z* $[M]^+$ Calcd for $C_9H_6Br_2FNO$: 320.8800 ; found:320.8797.

*4.2.6. 4-(Dibromofluoromethyl)-2-methylbenzonitrile (**8f**)*. The reaction was carried out according to the general procedure using 4-bromo-2-methylbenzonitrile as Ar–X except for using 2.12 equiv. of *i*-PrMgBr. Yellow oil (36.9 mg, 12%). IR (neat): 2231, 1738, 1564, 1491, 1446, 1392, 1385, 1282, 1209, 1124, 1034, 939, 833, 818, 754, 692 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, J = 8.8 Hz, 1H), 7.57–7.55 (m, 2H), 2.69 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.3 (d, J = 18.6 Hz, 1C), 136.4 (d, J = 2.7 Hz, 1C), 136.2 (s, 1C), 129.5 (d, J = 2.3 Hz, 1C), 124.9 (s, 1C), 117.6 (s, 1C), 114.5 (s, 1C), 88.6 (d, J = 313.7 Hz, 1C), 20.9 (s, 1C). ^{19}F NMR (376 MHz, $CDCl_3$): δ –50.4 (s, 1F). GCMS-EI: *m/z* 228 $[M+2–Br]^+$ (95.1), 226 $[M–Br]^+$ (100), 147 $[M–2Br]^+$ (86.3), 116 $[M–CBr_2F]^+$ (0.9). HRMS-FAB: *m/z* $[M+H]^+$ Calcd for $C_9H_7Br_2FN$: 305.8929; found: 305.8929.

*4.2.7. 4-(Dibromofluoromethyl)-3-methylbenzonitrile (**8g**)*. The reaction was carried out according to the general procedure using 4-bromo-3-methylbenzonitrile as Ar–X. Yellow oil (65.1 mg, 22%). IR (neat): 2231, 1560, 1489, 1456, 1394, 1282, 1209, 1124, 1034, 939, 889, 833, 818, 758, 692 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, J = 8.8 Hz, 1H), 7.58–7.54 (m, 2H), 2.69 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.3 (d, J = 18.4 Hz, 1C), 136.4 (d, J = 2.8 Hz, 1C), 136.3 (s, 1C), 129.5 (d, J = 2.2 Hz, 1C), 124.8 (s, 1C), 117.6 (s, 1C), 114.5 (s, 1C), 88.6 (d, J = 313.7 Hz, 1C), 20.9 (s, 1C). ^{19}F NMR (376 MHz, $CDCl_3$): δ –50.4 (s, 1F). GCMS-EI: *m/z* 228 $[M+2–Br]^+$ (98.1), 226

$[M–Br]^+$ (100), 147 $[M–2Br]^+$ (81.8), 116 $[M–CBr_2F]^+$ (0.9), 90 $[M–CN–CBr_2F]^+$ (0.8). HRMS-FAB: *m/z* $[M+H]^+$ Calcd for $C_9H_7Br_2FN$: 305.8929; found: 305.8936.

*4.2.8. Methyl 4-(dibromofluoromethyl)benzoate (**8i**).* The reaction was carried out according to the general procedure using methyl 4-iodobenzoate as Ar–X. White solid (90.9 mg, 28%). mp. 39.2–41.9 °C. IR (neat): 2952, 1722, 1435, 1408, 1275, 1221, 1109, 1049, 1018, 872, 818, 785, 721, 681 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.09 (d, J = 8.6 Hz, 2H), 7.73 (d, J = 8.6 Hz, 2H), 3.95 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.8 (s, 1C), 148.3 (d, J = 20.4 Hz, 1C), 132.0 (s, 1C), 129.7 (s, 2C), 124.2 (d, J = 6.9 Hz, 2C), 89.5 (d, J = 314.7 Hz, 1C), 52.5 (s, 1C). ^{19}F NMR (376 MHz, $CDCl_3$): δ –56.4 (s, 1F). GCMS-EI: *m/z* 297 $[M+4–OMe]^+$ (2.5), 295 $[M+2–OMe]^+$ (5.3), 293 $[M–OMe]^+$ (2.7), 247 $[M+2–Br]^+$ (97.8), 245 $[M–Br]^+$ (100), 214 $[M–Br–OMe]^+$ (9.5), 135 $[M–CBr_2F]^+$ (1.0). HRMS-FAB: *m/z* $[M+H]^+$ Calcd for $C_9H_8Br_2FO_2$: 324.8875; found: 324.8876.

*4.2.9. 1-(Dibromofluoromethyl)-4-(pentafluorosulfanyl)benzene (**8j**).* The reaction was carried out according to the general procedure using 1-iodo-4-(pentafluorosulfanyl)benzene as Ar–X. White gam (127.1 mg, 32%). IR (neat): 1410, 1232, 1201, 1103, 1053, 808, 750, 696, 656 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.83 (d, J = 9.0 Hz, 2H), 7.76 (d, J = 9.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.9 (qui, J = 18.1 Hz, 1C), 147.3 (d, J = 21.0 Hz, 1C), 126.3 (qui, J = 4.6 Hz, 2C), 124.7 (d, J = 7.1 Hz, 2C), 88.3 (d, J = 314.3 Hz, 1C). ^{19}F NMR (376 MHz, $CDCl_3$): δ –81.4 (qui, J = 150.7 Hz, 1F), –61.3 (d, J = 150.7 Hz, 4F), –57.4 (1F).

GCMS-EI: *m/z* 315 $[M+2–Br]^+$ (100), 313 $[M–Br]^+$ (97.3). HRMS-EI: *m/z* $[M]^+$ Calcd for $C_7H_4Br_2F_6S$: 391.8305; found: 391.8309.

*4.2.10. 4-(Dibromofluoromethyl)phenyl 4-methylphenyl sulfone (**8k**).* The reaction was carried out according to the general procedure using 4-iodophenyl 4-methylphenyl sulfone as Ar–X. White solid (132.0 mg, 31%). mp. 158.8–160.3 °C. IR (neat): 1603, 1495, 1286, 1246, 1203, 1165, 1136, 1036, 958, 804, 777, 715, 652 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.97 (d, J = 8.4 Hz, 2H), 7.85 (d, J = 8.4 Hz, 2H), 7.76 (d, J = 8.5 Hz, 2H), 7.34 (d, J = 8.5 Hz, 2H), 2.42 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.4 (d, J = 21.0 Hz, 1C), 144.8 (s, 1C), 144.0 (s, 1C), 137.8 (s, 1C), 130.2 (s, 2C), 128.0 (s, 2C), 127.7 (s, 2C), 125.1 (d, J = 7.0 Hz, 2C), 88.6 (d, J = 314.7 Hz, 1C), 21.6 (s, 1C). ^{19}F (376 MHz, $CDCl_3$): δ –57.3 (s, 1F). GCMS-EI: *m/z* 343 $[M+2–Br]^+$ (37.4), 341 $[M–Br]^+$ (36.8), 139 $[MeC_6H_4SO]^+$ (100), 91 $[MeC_6H_4]^+$ (19.2), 77 $[C_6H_5]^+$ (10.8). HRMS-FAB: *m/z* $[M+H]^+$ Calcd for $C_{14}H_{12}Br_2FO_2S$: 420.8909; found: 420.8910.

*4.2.11. 4-(Dibromofluoromethyl)phenyl 4-fluorophenyl sulfone (**8l**).* The reaction was carried out according to the general procedure using 4-fluorophenyl 4-iodophenyl sulfone as Ar–X. White solid (207.0 mg, 49%). mp. 91.1–92.8 °C. IR (neat): 1589, 1491, 1402, 1323, 1290, 1240, 1217, 1161, 1149, 1097, 1047, 870, 847, 820, 756, 727, 692, 658 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.02–7.96 (m, 4H), 7.79 (d, J = 8.7 Hz, 2H), 7.22 (dd, J = 8.5, 8.7 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.8 (d, J = 255.5 Hz, 1C), 148.7 (d, J = 21.1 Hz, 1C), 143.5 (s, 1C), 136.8 (d, J = 3.0 Hz, 2C), 130.8 (d, J = 9.5 Hz, 2C), 127.8 (s, 2C), 125.2 (d, J = 7.2 Hz, 1C), 116.9 (d, J = 22.6 Hz, 2C), 88.4 (d, J = 314.7 Hz, 1C). ^{19}F NMR (376 MHz, $CDCl_3$): δ –56.5 (s, 1F), –104.3 (m, 1F).

GCMS-EI: *m/z* 347 $[M+2–Br]^+$ (43.8), 345 $[M–Br]^+$ (43.6), 143 $[FC_6H_4SO]^+$ (100), 95 $[FC_6H_4]^+$ (22.9). HRMS-FAB: *m/z* $[M+H]^+$ Calcd for $C_{13}H_9Br_2F_2O_2S$: 424.8658; found: 424.8655.

*4.2.12. 2-Bromo-1,3-dichloro-5-(dibromofluoromethyl)benzene (**8m**)*. The reaction was carried out according to the general procedure using 2-bromo-1,3-dichloro-5-iodobenzene as Ar–X. Yellow oil (88.6 mg, 21%). IR (neat): 1549,1417, 1375, 1228, 1196, 1066, 1024, 947, 877, 810, 744, 717, 694 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.65 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.8 (d, J =21.9 Hz, 1C), 133.6 (s, 2C), 126.2 (s, 1C), 124.0 (d, J = 7.3 Hz, 2C), 86.7 (d, J = 314.7 Hz, 1C). ^{19}F NMR (376 MHz, $CDCl_3$): δ –57.6 (s, 1F). GCMS-EI: *m/z* 418 [M+6] (0.9), 416 [M+4] (1.5), 414 [M+2] (1.1), 339 $[M+6–Br]^+$ (31.0), 337 $[M+4–Br]^+$ (88.0), 335 $[M+2–Br]^+$ (100), 333 $[M–Br]^+$ (38.7), 223 $[M–CBr_2F]^+$ (1.8). HRMS-EI: *m/z* $[M]^+$ Calcd for $C_7H_2Br_3Cl_2F$: 411.7068; found: 411.7064.

*4.2.13. 4-(Dibromofluoromethyl)benzotrifluoride (**8n**)*. The reaction was carried out according to the general procedure using 4-iodobenzotrifluoride as Ar–X. Orange oil (20.0 mg, 6%). IR (neat): 1412, 1323, 1221, 1171, 1130, 1122, 1068, 1018, 872, 850, 762, 706, 669 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.79 (d, J = 8.4 Hz, 2H), 7.69 (d, J = 8.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.7 (d, J =20.9 Hz, 1C), 132.5 (q, J = 33.0 Hz, 1C), 125.6 (q, J = 3.4 Hz, 2C), 124.6 (d, J = 7.0 Hz, 2C), 123.4 (q, J = 270.7 Hz, 1C), 89.0 (d, J = 314.4 Hz, 1C). ^{19}F NMR (376 MHz, $CDCl_3$): δ –56.8 (s, 1F), –64.3 (s, 3F). GCMS-EI: *m/z* 319 $[M+4–F]^+$ (0.6), 317 $[M+2–F]^+$ (1.3), 315 $[M–F]^+$ (0.7), 257

$[M+2–Br]^+$ (95.9), 255 $[M–Br]^+$ (100), 238 $[M+2–Br–F]^+$ (5.2), 236 $[M–Br–F]^+$ (5.4). HRMS-EI: *m/z* $[M]^+$ Calcd for $C_8H_4Br_2F_4$: 333.8616; found: 333.8608.

*4.2.14. 5-(Dibromofluoromethyl)-2-(trifluoromethyl)pyridine (**8o**).* The reaction was carried out according to the general procedure using 5-bromo-2-(trifluoromethyl)pyridine as Ar–X. Colorless oil (82.0 mg, 24%). IR (neat): 1389, 1335, 1254, 1180, 1138, 1088, 1053, 1020, 874, 783, 775, 733, 688cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.04 (d, J = 2.2 Hz, 1H), 8.14 (dd, J = 2.2, 8.4 Hz, 1H), 7.77 (d, J = 8.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.7 (q, J = 35.3 Hz, 1C), 145.7 (d, J = 7.3 Hz, 1C), 142.8 (d, J = 21.1 Hz, 1C), 133.4 (d, J = 6.4 Hz, 1C), 120.9 (q, J = 272 Hz, 1C), 120.1(s, 1C), 86.3 (d, J = 314 Hz, 1C). ^{19}F NMR (376 MHz, $CDCl_3$): δ –59.2 (s, 1F), –69.4 (s, 3F). GCMS-EI: *m/z* 320 $[M+4–F]^+$ (0.6), 318 $[M+2–F]^+$ (1.4), 316 $[M–F]^+$ (0.7), 258 $[M+2–Br]^+$ (96.8), 256 $[M–Br]^+$ (100), 239 $[M+2–Br–F]^+$ (4.9), 237 $[M–Br–F]^+$ (5.0). HRMS-EI: *m/z* $[M]^+$ Calcd for $C_7H_3Br_2F_4N$: 334.8568; found: 334.8564.

*4.3. Reaction of 4-(dibromofluoromethyl)phenyl 4-methylphenyl sulfone (**8k**) in 1M aqueous NaOH to (p-tolylsulfonyl)benzoic acid (**9**) [19].*

A solution of 4-(dibromofluoromethyl)phenyl 4-methylphenyl sulfone (**8k**) (20.0 mg, 0.047 mmol) in THF (1.0 mL) and 1M aq. NaOH (1.0 mL) was heated at 50 °C for 36 h. The reaction mixture was neutralized with 1M aq. HCl (1.9 mL) and extracted with EtOAc (2.0 mL x 3). The combined extracts were dried over Mg_2SO_4. Concentration of the solvent in vacuo afforded **9** as a white solid (13.4 mg, quant.). ^{1}H

NMR (400 MHz, DMSO-d_6) δ 13.5 (brs, 1H), 8.12 (d, J = 8.7 Hz, 2H), 8.05 (d, J = 8.7 Hz, 2H), 7.87 (d, J = 8.3 Hz, 2H), 7.45 (d, J = 8.3 Hz, 2H), 2.38 (s, 3H).

*4.4. Preparation of 4-(bromofluoromethyl)phenyl 4-methylphenyl sulfone (**10**).*

To a stirred solution of 4-(dibromofluoromethyl)phenyl 4-methylphenyl sulfone (**8k**) (50.0 mg, 0.12 mmol) in EtOH (1.0 mL) was added $NaBH_4$ (9.7 mg, 0.24 mmol) at room temperature under Ar and the resulting mixture was stirred for 2 h. The reaction mixture was quenched with 1M aq. HCl (2.0 mL) and extracted with EtOAc (10 mL x 3). The combined extracts were dried over $MgSO_4$. Concentration of the solvent in vacuo afforded a residue, which was purified by silica gel column chromatography (hexane/EtOAc = 3/1) to give **10** (26.5 mg, 65%) as a white solid. IR (neat): 1595, 1414, 1315, 1292, 1219, 1190, 1151, 1103, 1072, 1030, 1016, 968, 887, 839, 810, 708, 690, 658, 625 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.98 (d, J = 8.2 Hz, 2H), 7.84 (d, J = 8.2 Hz, 2H), 7.61 (d, J = 8.6 Hz, 2H), 7.40 (d, J = 49.3 Hz, 1H), 7.32 (d, J = 8.6 Hz, 2H), 2.41 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.3 (s, 1C), 141.6 (d, J = 17.3 Hz, 1C), 138.5 (s, 2C), 130.0 (s, 2C), 127.9 (s, 2C), 127.7 (s, 2C), 127.2 (d, J = 6.8 Hz, 2C), 83.2 (d, J = 169.0 Hz, 1C), 21.6 (s, 1C). ^{19}F NMR (376 MHz, $CDCl_3$): δ –136.7 (d, J = 46.2 Hz, 1C). HRMS-EI: *m/z* $[M]^+$ Calcd for $C_{14}H_{12}BrFO_2S$: 341.9725; found: 341.9728.

*4.5. Preparation of 4-(fluoromethyl)phenyl 4-methylphenyl sulfone (**11**).*

To a stirred solution of 4-(dibromofluoromethyl)phenyl 4-methylphenyl sulfone (**8k**) (50.0 mg, 0.12 mmol) in toluene (2.0 mL) was added *n*-Bu_3SnH (125 µl, 0.47 mmol) and 2,2'-azobisisobutyronitrile (AIBN, 9.7 mg, 59 µmol) and the resulting mixture was heated at 100 °C for 12 h. The reaction mixture was cooled down to room

temperature, diluted with H_2O (5 mL), and extracted with EtOAc (10 mL x 3). The combined extracts were dried over $MgSO_4$. Concentration of the solvent in vacuo afforded a residue, which was purified by silica gel column chromatography (hexane/EtOAc = 3/1) to give **11** (31.1 mg, quant.) as a white solid. IR (neat): 2922, 1595, 1412, 1375, 1317, 1213, 1153, 1105, 978, 810, 796, 739, 706, 671, 646 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.95 (d, J = 8.3 Hz, 2H), 7.83 (d, J = 8.3 Hz, 2H), 7.47 (d, J = 8.0 Hz, 2H), 7.30 (d, J = 8.0 Hz, 2H), 5.42 (d, J = 46.9 Hz, 2H), 2.40 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.3 (s, 1C), 141.6 (d, J = 17.3 Hz, 1C), 138.5 (s, 2C), 130.0 (s, 2C), 127.9 (s, 2C), 127.7 (s, 2C), 127.2 (d, J = 6.8 Hz, 2C), 83.2 (d, J = 169.0 Hz, 1C), 21.6 (s, 1C). ^{19}F NMR (376 MHz, $CDCl_3$): δ –215.8 (t, J = 46.9 Hz, 1F). GCMS-EI: *m/z* 264 $[M]^+$ (72.6), 155 $[MeC_6H_4SO_2]^+$ (6.1), 139 $[MeC_6H_4SO]^+$ (100), 91 $[MeC_6H_4]^+$ (63.5). HRMS-FAB: *m/z* $[M+H]^+$ Calcd for $C_{14}H_{14}FO_2S$: 265.0699; found: 265.0700.

*4.6. Preparation of 4-[fluorobis(4-nitrophenyloxy)methyl]phenyl 4-methylphenyl sulfone (**12**).*

To a stirred solution of 4-(dibromofluoromethyl)phenyl 4-methylphenyl sulfone (**8k**) (80.0 mg, 0.19 mmol) in DMF (2.0 mL) was added 4-nitrophenol (58.2 mg, 0.42 mmol) and K_2CO_3 (78.8 mg, 0.57 mmol) at room temperature under Ar and the resulting mixture was heated at 100 °C for 12 h. The reaction mixture was cooled down to room temperature, diluted with H_2O (5 mL), and extracted with EtOAc (10 mL x 3). The combined extracts were dried over $MgSO_4$. Concentration of the solvent in vacuo afforded a residue, which was purified by silica gel column chromatography (hexane/EtOAc = 3/1) to give **12** (71.3 mg, 70%) as a light-yellow solid. IR (neat): 1612,

1591, 1518, 1512, 1489, 1342, 1325, 1294, 1273, 1236, 1157, 1099, 1038, 1012, 852, 814, 744, 731, 663, 609 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.16 (d, J = 9.2Hz, 4H), 8.00 (d, J = 8.4 Hz, 2H), 7.82 (d, J = 8.2 Hz, 2H), 7.80 (d, J = 8.4 Hz, 2H), 7.33 (d, J = 8.2 Hz, 2H), 7.22 (d, J = 9.2 Hz, 4H), 2.42 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.0 (s, 2C), 145.0 (s, 1C), 144.9 (s, 1C), 144.6 (s, 2C), 138.2 (d, J = 33.5 Hz, 1C), 137.6 (s, 1C), 130.2 (s, 2C), 128.1 (s, 2C), 128.0 (s, 2C), 127.5 (d, J = 4.5 Hz, 2C), 125.5 (s, 4C), 127.0 (s, 4C), 119.3 (d, J = 255.2 Hz, 1C), 21.6 (s, 1C). ^{19}F NMR (376 MHz, $CDCl_3$): δ –74.2 (s, 1F). HRMS-FAB: *m/z* $[M+H]^+$ Calcd for $C_{26}H_{20}FN_2FO_8S$: 539.0924; found: 539.0927.

*4.7. Preparation of 2-fluoro-2-[4-(4-methylphenylsulfonyl)phenyl]-2H-dibenzo[d,f][1,3]dioxepin (**13**).*

To a stirred solution of 4-(dibromofluoromethyl)phenyl 4-methylphenyl sulfone (**8k**) (80.0 mg, 0.19 mmol) in DMF (1.0 mL) was added 2,2'-dihydroxybiphenyl (38.9 mg, 0.21 mmol) and K_2CO_3 (78.8 mg, 0.57 mmol) at room temperature under Ar and the resulting mixture was heated at 100 °C for 12 h. The reaction mixture was cooled down to room temperature, diluted with H_2O (5 mL), and extracted with EtOAc (10 mL x 3). The combined extracts were dried over $MgSO_4$. Concentration of the solvent in vacuo afforded a residue, which was purified by silica gel column chromatography (hexane/EtOAc = 3/1) to give **13** (56.8 mg, 67%) as a colorless solid. IR (neat): 1595, 1502, 1479, 1439, 1398, 1323, 1286, 1252, 1153, 1097, 1057, 1039, 1012, 812, 764, 756, 721, 660 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.97 (d, J = 8.4 Hz, 2H), 7.83 (d, J = 8.4 Hz, 2H), 7.81 (d, J = 8.6 Hz, 2H), 7.58 (dd, J = 1.8, 7.5 Hz, 2H), 7.37 (td, J = 1.3, 7.5 Hz, 2H), 7.34–7.28 (m, 4H), 7.00 (dd, J = 1.3, 7.8 Hz, 2H), 2.41 (s, 3H). ^{13}C NMR

(100 MHz, $CDCl_3$): δ 149.2 (s, 2C), 144.5 (s, 1C), 143.7 (s, 1C), 139.9 (d, J = 35.1 Hz, 1C), 138.1 (s, 1C), 131.3 (s, 2C), 130.0 (s, 2C), 130.0 (s, 2C), 129.0 (s, 2C), 128.3 (s, 2C), 127.9 (s, 2C), 127.5 (s, 2C), 127.1 (d, J = 3.7 Hz, 2C), 127.1 (d, J = 240 Hz, 1C), 122.7 (s, 2C), 21.6 (s, 1C). ^{19}F NMR (376 MHz, $CDCl_3$): δ –67.9 (s, 1F). HRMS-FAB: *m/z* $[M+H]^+$ Calcd for $C_{26}H_{20}FO_4S$: 447.1066; found: 447.1077.

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