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Note

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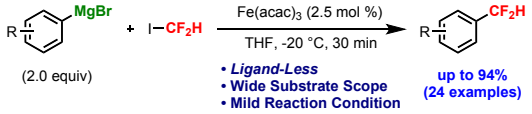
Ligand-Less Iron-Catalyzed Aromatic Cross-Coupling Difluoromethylation of Grignard Reagents with Difluoroiodomethane

Hirotaka Motohashi, Miki Kato, and Koichi Mikami*

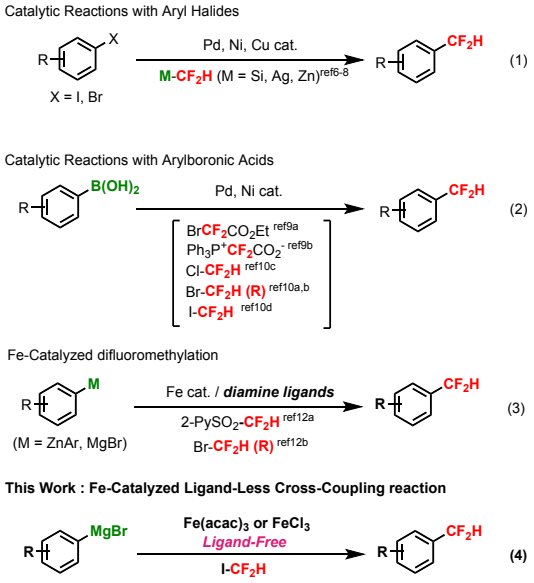
Department of Chemical Science and Engineering, School of Materials and Chemical Technology, Tokyo Institute of Technology, O-okayama, Meguro-ku, Tokyo 152-8552 (Japan)



ABSTRACT: Iron-catalyzed cross-coupling difluoromethylations of the Grignard reagents with difluoroiodomethane provide various aromatic difluoromethyl products in good yields, *not employing sterically demanding ligands*. Difluoromethylations proceed within 30 min at -20 °C with 2.0 equiv of the Grignard reagents and $FeCl_3$ or $Fe(acac)_3$ (2.5 mol %). Mechanistic investigations clarify difluoromethyl radical intervention; Fe(0) ate is initially generated. Single electron transfer from Fe(0) ate to difluoroiodomethane takes place. Recombination with aryl groups gives Ar-CF_2Hs. The catalyst can be regenerated by the Grignard reagents.

Recently, organofluorine functional groups have been widely applied in pharmaceutical and agrochemical design because of their unique chemical and physical properties such as high polar effect, metabolic stability, mimic effect, and lipophilicity.[1] Among them, difluoromethyl group is regarded as a key bioisostere of alcohol and as a lipophilic hydrogen bonding donor.[2] Due to its high demand, methods of introducing a difluoromethyl group into an aromatic core to give difluoromethyl arenes of synthetic importance have been intensively developed.[3] In recent years, direct carbon-carbon bond forming reactions were reported.[4,5] However, transition metal-catalyzed difluoromethylation is quite limited; Difluoromethylation using difluoromethyl metal species such as Si, Ag and Zn reagents by Pd, Ni, and Cu catalysts have been reported (Scheme 1, eq 1).[6-8] However, the difluoromethyl metal species are thermally unstable at high reaction temperatures. Subsequently, reactions using difluoromethyl halides as electrophiles were reported; A metal-difluorocarbene[9] or Suzuki-Miyaura reactions[10] of arylboronic acids catalyzed by palladium or nickel were reported (Scheme 1, eq 2). Recently, we reported the nickel-catalyzed Kumada-Tamao-Corriu reaction using the Grignard reagent as a nucleophile.[11] Quite recently, difluoromethylation reactions using iron/ligand complexes have also been reported with limited substrate scope (Scheme 1, eq 3).[12] However, a conceptual challenge in *ligand-less* iron-catalyzed difluoromethylation of wide substrate scope *without sterically demanding ligand* has not yet been described. Here, we uncover the *ligand-free* iron-catalyzed difluoromethylation of the Grignard reagents with difluoroiodomethane. The mechanism is uncovered to involve CF_2H radical species.

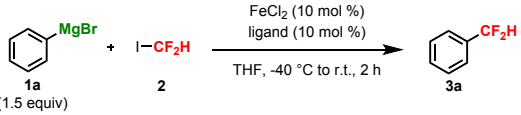
Scheme 1. Transition-Metal-Catalyzed Aromatic Difluoromethylations



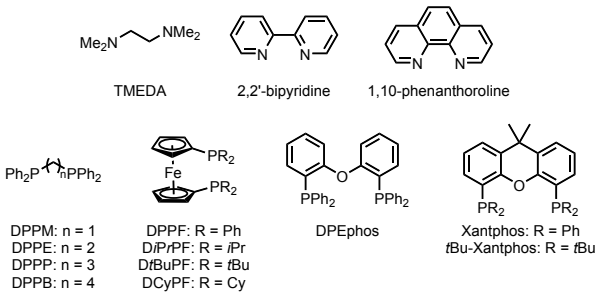
An iron-catalyzed difluoromethylation of phenylmagnesium bromide **1a** with difluoroiodomethane **2** was investigated first with 10 mol% of $FeCl_2$ through ligand screening (Table 1). Without any iron catalyst, no difluoromethylation proceeded with aromatic Grignard reagents **1** and difluoroiodomethane **2**. Some of diamine ligands gave the desired difluoromethylation product **3a**, however, in only poor yield (Entry 1-3). Various diphosphine ligands including diphenylphosphinoalkane (Entry 4-7), disubstituted phosphinoferrocene (Entry 8-11) and xanthen-derived ligands (Entry 12-14) did not show a drastic improvement of yield. Delightfully, we found that the *ligand-*

less iron-catalyzed cross-coupling difluoromethylation could proceed to afford **3a** in the highest yield (Entry 15).

Table 1. Screening of Ligands



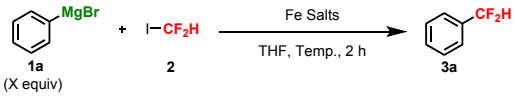
Entry	Ligand	Yield (%)
1	TMEDA	5
2	2,2'-bipyridine	2
3	1,10-phenanthoroline	5
4	DPPM	15
5	DPPE	8
6	DPPP	8
7	DPPB	2
8	DPPF	20
9	D*i*PrPF	38
10	D*t*BuPF	15
11	DCyPF	25
12	DPEphos	30
13	Xantphos	35
14	*t*Bu-Xantphos	33
15	-	40



[a] Yields were determined by ^{19}F NMR analysis using benzotrifluoride as an internal standard.

Subsequently, optimization of reaction conditions was carried out by screening various Fe salts (Table 2). Better yields (55 and 58%) were observed with $FeCl_3$ and $Fe(acac)_3$ (Ferric acetylacetonate) (Entry 1-4). $Fe(acac)_3$ has been reported to show better reproducibility than $FeCl_3$.[13] Therefore, we decided to focus on $Fe(acac)_3$. Increase in the amount of **1a** to 2.0 equiv showed improvement in yield to 68%. However, further increase in the amount of **1a** did not raise yields (Entry 5-7). The temperature, at which **1a** was added, was next examined to show that -20 ℃ was the best (Entry 8-10). A significant improvement in yield was observed when phenylmagnesiumbromide **1a** was dropwised over 30 min (Entry 11-13). The best conditions were thus set to give up to 92% yield; The amount of catalyst and reaction time were reduced to 2.5 mol% and 30 min, respectively (Entry 12-13).

Table 2. Optomization of Reaction Conditions

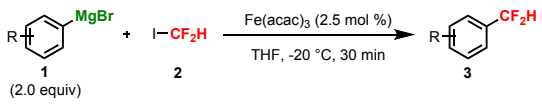


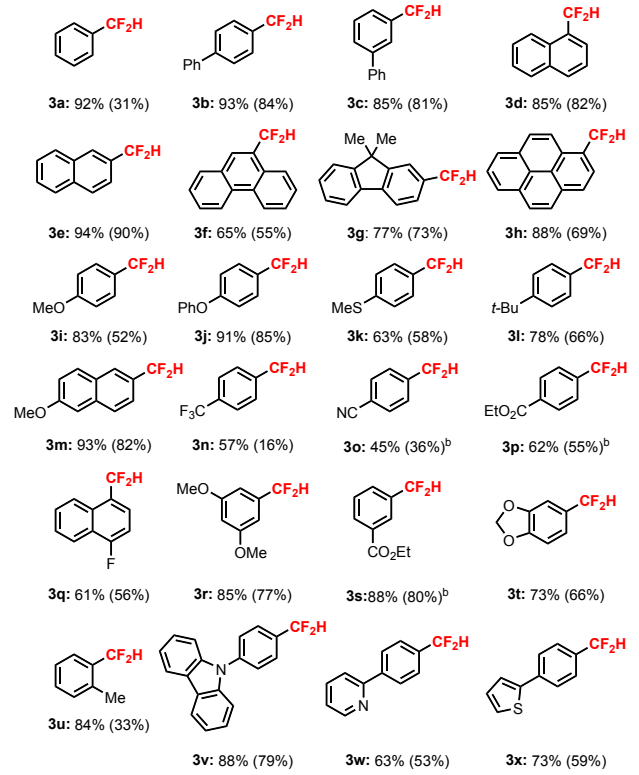
Entry	X (equiv)	Fe Salt (mol %)	Temp	Yield (%)
1	1.5	$FeCl_2$ (10)	-40 °C to rt	40
2	1.5	$FeCl_3$ (10)	-40 °C to rt	55
3	1.5	FeF_3 (10)	-40 °C to rt	0
4	1.5	$Fe(acac)_3$ (10)	-40 °C to rt	58
5	2.0	$Fe(acac)_3$ (10)	-40 °C to rt	68
6	2.5	$Fe(acac)_3$ (10)	-40 °C to rt	63
7	3.0	$Fe(acac)_3$ (10)	-40 °C to rt	40
8	2.0	$Fe(acac)_3$ (10)	-78 °C to rt	28
9	2.0	$Fe(acac)_3$ (10)	-20 °C to rt	72
10	2.0	$Fe(acac)_3$ (10)	0 °C to rt	45
11[b]	2.0	$Fe(acac)_3$ (10)	-20 °C to rt	79
12[b]	2.0	$Fe(acac)_3$ (5.0)	-20 °C to rt	87
13[b,c]	2.0	$Fe(acac)_3$ (2.5)	-20 °C	92

[a] Yields were determined by ^{19}F NMR analysis using benzotrifluoride as an internal standard.
[b] Phenylmagnesiumbromide **1a** was dropwised over 30 min.
[c] The reaction time was 30 min.

Substrate scope was clarified under the optimized reaction conditions (2.5 mol% of $Fe(acac)_3$, -20 ℃ , 30 min) (Table 3). Difluoromethylated aryls were thus synthesized without deprotonation via cross-coupling difluoromethylation with a variety of the Grignard reagents **1**. Sterically demanding biphenyl, naphthyl, phenanthryl, fluorenyl and pyrenylmagnesium bromide afforded difluoromethylated aryl products **3b-h** in good to excellent yields, by virtue of *ligand-free* conditions. Significantly, electron-withdrawing and even further functionalized hence reactive cyano and alkoxycarbonyl groups at not only *para*- but also *meta*-positions gave equally high or only slightly reduced yields (**3n-q**, and **s**). Electron-donating substituents in *para*-position provided high reactivity to give products **3i-m** in good yields. Methoxy and 1,2-methylenedioxy substituents at *meta*-position also provided high yields (**3r** and **t**). High yield was also provided with sterically demanding *ortho*-substituted compound **3u**. Heteroaryl-substituted **1v-x** afforded products **3v-x** in reasonably good yields.

Table 3. Fe-Catalyzed Difluoromethylation with Grignard Reagents

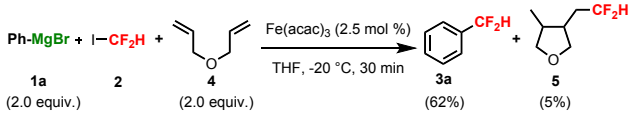




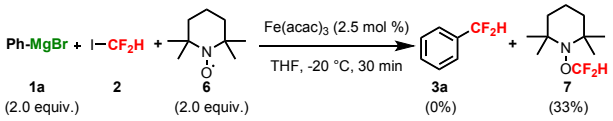
[a] Reaction conditions: 0.4 mmol of diluoroiodomethane (1.5-1.8 M), 0.8 mmol of ArMgBr (ca.0.8 M), 2.5 mol % of $Fe(acac)_3$ in 4 mL of THF. Yields were determined by ^{19}F NMR analysis using benzotrifluoride as an internal standard. Isolated yields are given in parenthesis.
[b] ArMgBr prepared from ArI with *i*PrMgBr.

Scheme 2. Investigation of Reaction Mechanism

Radical Cyclization



Radical Capture



[a] Yields were determined by ^{19}F NMR analysis using benzotrifluoride as an internal standard.

The reaction mechanism of an iron-catalyzed coupling reaction is challenging.[14-17] A radical clock experiment was first conducted;[10] When 2.0 equiv of radical clock **4** was added to the standard catalytic reaction, ring-closing product **5**[11] was formed and a decrease in yield of **3a** to 62% was confirmed (Scheme 2, eq 1). When 2.0 equiv of TEMPO (2,2,6,6-tetramethylpiperidine 1-oxyl) **6** was added to the standard catalytic reaction, the difluoromethylated aryl product **3a** was not observed at all and the CF_2H radical adduct of TEMPO **7**[18] was obtained in 33% yield (Scheme 2, eq 2).

Based on these results, the difluoromethyl radical is clarified to involve in this catalytic cycle. However, many types of Fe-catalysis cycle have been advocated for radical reactions. Therefore, we categorized the reported catalytic cycles to clarify the present reaction mechanism (Figure 1).

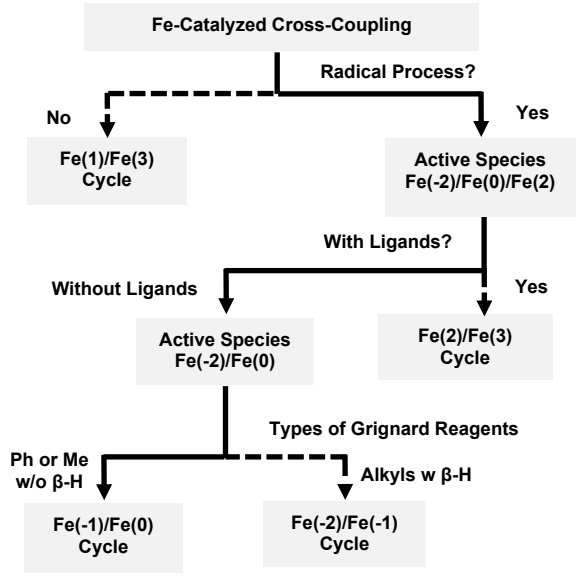
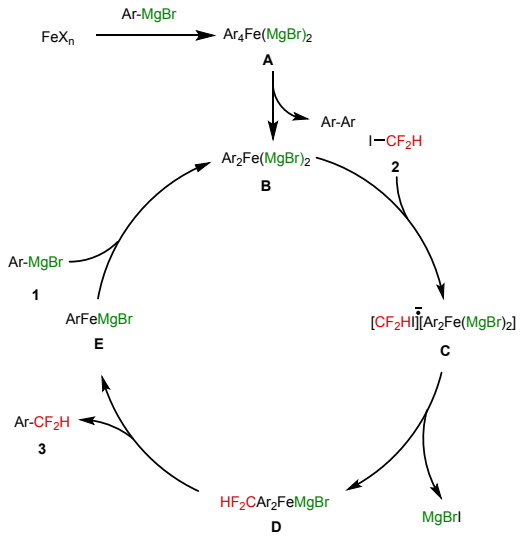


Figure 1. Classification of Fe-Catalyzed Mechanisms

First, reaction mechanisms are roughly divided into radical or non-radical mechanisms. When radicals are not involved, Fe(1)/Fe(3)[14] cycle is proposed. On the other hand, Fe(2), Fe(0), Fe(-2) species are reported as active species for radical mechanisms. The radical reaction mechanisms are further classified with or without a ligand. With a ligand, a cycle of Fe(2)/Fe(3) is proposed.[15] It has been reported that Fe(0) or Fe(-2) are formed as active species when a ligand is not bound to iron, depending on the type of Grignard reagents used; With an alkyl magnesium halide with β-hydride, an "inorganic Grignard reagent" of $Fe(MgX)_2$ is the composition formulated.[16] On the other hand, phenyl and methyl magnesium halides not bearing β-hydride are reported to involve Fe(0) ate complex as an active species.[13,16b,c,17] In the present reaction system, the formation of CF_2H radicals is confirmed and the coupling reaction was conducted with the aromatic Grignard reagents without β-hydride. Hence, Fe(0) ate ligand-free cycle is highly likely.

Scheme 3. Proposed Catalytic Cycles



The plausible mechanism is thus visualized in Scheme 3. First, Fe(2) complex **A** is reported to form by transmetalation of the aromatic Grignard reagents to the catalyst precursor $Fe(acac)_3$.[13,17d,e] A rapid reductive elimination of one molecule of biaryl, as observed in the crude mixture, from **A** produces Fe(0) ate complex **B** as an active species. However, **B** is formalism based on no free difluoromethyl radical coupling observed. Subsequently, single electron transfer to difluoroiodomethane **2** proceeds to give a Fe(1) complex **C** and difluoromethyl radical anion. After elimination of the magnesium salt from **C**, the difluoromethyl aromatic product is obtained by recombination of the CF_2H radical and the aryl group on **D** to eventually give the Fe(0) complex **E**. The active species **B** regenerates by addition of the Grignard reagents **1** to **E**.

In summary, we have succeeded in the cross-coupling difluoromethylation of organomagnesium reagents with difluoroiodomethane by the *ligand-less* Fe catalyst under the mild reaction conditions to give a wide scope of substrates without sterically demanding ligand.

EXPERIMENTAL SECTION

Synthetic Procedure of Difluoroiodomethane (2) from Chlorodifluoroacetic Acid[19]

KI (99.6 g, 0.6 mol), CuI (57.1 g, 0.3 mol), and DMF (250 mL, containing water 1.5 mL) were placed in a 1 L three-necked round-bottomed flask equipped reflux condenser with a trap (trap was cooled to -78 °C) under nitrogen atmosphere. To a solution of them was added chlorodifluoroacetic acid (25 mL, 0.3 mol) in DMF (25 mL) dropwise during 0.5 h at 90 °C. After the reaction temperature was warmed up in 10 °C every an hour up to 140 °C, difluoroiodomethane was collected in a trap (8.0 g, 15% yield). Because of the low boiling point (21-23 °C, condition: 20 °C, 1 atm) of difluoroiodomethane, THF solution of difluoroiodomethane was used. The concentration of THF solution (1.2-1.8 M) was determined by ^{19}F NMR analysis using BTF as an internal standard.

^1H NMR (300 MHz, $CDCl_3$) δ 7.47 (t, J_{H-F} = 55.8 Hz); ^{13}C {^1H} NMR (75 MHz, $CDCl_3$) δ 84.1 (t, J_{C-F} = 305.0 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ -68.0 (d, J_{F-H} = 56.2 Hz).

Preparation of Grignard Reagents

Phenylmagnesiumbromide **1a** was purchased from Sigma Aldrich. Grignard reagents **1a-n**, **1r**, **1q-r**, and **1t-x** were prepared by the reaction of the corresponding Ar-Br and Mg turnings in THF (ca. 0.5 M). In contrast, Grignard reagents **1o-q**, **1s** were prepared by the reaction of the corresponding Ar-I and ^{i}PrMgBr in THF according to previous report[20]. 2-(4-bromophenyl)pyridine and 2-(4-bromophenyl)thiophene for preparing **1w** and **1x** were synthesized according to previous report[21,22].

Synthetic Procedure for The Preparation of 2-(4-bromophenyl)pyridine and 2-(4-bromophenyl)thiophene

1) Synthesis of Arylboronic Acids[21]

To a solution of 1,4-dibromobenzene (7.1 g, 30 mmol) in THF (100 mL) was added dropwise *n*-BuLi (2.6 M, 35 mmol, 13.5 mL) at -78 ℃ and stirred for 1 h. $B(OMe)_3$ (8.12 g, 78 mmol) was then added. The resulting mixture was stirred at -78 °C for further 1 h and then allowed to warm up to room temperature. The solution was acidified with 3 M HCl solution and extracted with Et_2O (100 mL×3). The combined organic layer was dried over $MgSO_4$ and evaporated to give slight yellow solid which was used without further purification. Thiophene-2-ylboronic acid was prepared in the same manner from thiophene.

2) Synthesis of 2-(4-bromophenyl)pyridine [21]

To a solution of 4-bromophenylboronic acid (1.5 g, 8.4 mmol), $Pd(PPh_3)_4$ (0.2 g, 0.2 mmol, 3 mol %) and Na_2CO_3 (5.0 g, 47.2 mmol) in toluene (24 mL), water (24 mL) and ethanol (10 mL) was added 2-bromopyridine (1.0 g, 6.4 mmol) under nitrogen atmosphere. The solution was refluxed for 20 h and cooled to room temperature. Water (30 mL) was added and the mixture was extracted with EtOAc (50 mL×3). The combined organic layer was dried over $MgSO_4$. The solvent was removed by evaporation and the residue was purified by silica-gel column chromatography (15% EtOAc in hexane) to afford the pure product. The product is known compound and the following data are identical to those given in corresponding literature.[23] ^1H NMR (300 MHz, CD_2Cl_2) δ 8.66 (d, 1H, J = 4.8 Hz), 7.94-7.91 (m, 2H), 7.75 (tt, 2H, J = 6.8 Hz, 1.6 Hz), 7.63-7.59 (m, 2H), 7.26 (ddd, 1H, J = 8.5 Hz, 4.8 Hz, 1.9 Hz); ^{13}C {^1H} NMR (75 MHz, CD_2Cl_2) δ 156.3, 150.1, 138.7, 137.2, 132.1, 128.8, 123.6, 122.9, 120.5.

3) Synthesis of 2-(4-bromophenyl)thiophene [22]

To a solution of thiophene-2-ylboronic acid (1.0 g, 7.5 mmol), $Pd(PPh_3)_4$ (0.35 g, 0.35 mmol, 5 mol %) and Na_2CO_3 (9.0 g, 85 mmol) in DME (30 mL) and water (45 mL) was added the solution of 1,4-bromoiodobenzene (1.7 g, 6.0 mmol) in DME (15 mL) under nitrogen atmosphere. The solution was refluxed for 12 h and cooled to room temperature. Water (15 mL) was added and the mixture was extracted with Et_2O (25 mL×3). The combined organic layer was dried over $MgSO_4$. The solvent was removed by evaporation. The crude was purified by recrystallization twice from ethanol to afford the pure product.

The product is known compound and the following data are identical to those given in corresponding literature.[24] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49-7.48 (m, 4H), 7.30 (d, 2H, J = 4.3 Hz), 7.10-7.07 (m, 1H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 143.2, 133.5, 132.1, 128.3, 127.5, 125.4, 123.6, 121.4.

General Procedure for Fe-Catalyzed Difluoromethylation

In an argon-filled glovebox, $Fe(acac)_3$ (3.5 mg, 0.001 mmol, 2.5 mol %) was added to 10 mL test tube. After the tube was sealed with a septum, THF (4 mL) was added. To this solution was added difluoroiodomethane **2** in THF (1.2-1.8 M, 220-330 μL, 0.40 mmol) at room temperature. The solution was cooled to -20 ℃ then, Grignard reagents **1** (ca. 0.5 M in THF, 1.6 mL, 0.8 mmol) was added dropwise over 30 min. After warmed up to at room temperature, the reaction mixture was quenched by saturated NH_4Cl aqueous solution, and Et_2O (5.0 mL) was added. The organic layer was separated, and the aqueous layer was extracted with Et_2O (5.0 mL × 3). The combined organic layer was evaporated. NMR yield was determined by using benzotrifluoride (BTF) as an internal standard. The resulting crude product was purified by silica-gel column chromatography to give difluoromethylated products **3**.

(Difluoromethyl)benzene (3a)
Colorless liquid. NMR yield (92%) was determined by using BTF as an internal standard. The residue was purified by silica-gel column chromatography (pentane only) to afford the compound (15.9 mg, 31% yield). The product is known compound and the following data are identical to those given in corresponding literature.[25] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53-7.45 (m, 5H), 6.65 (t, 1H, J_{H-F} = 56.5 Hz); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 134.5 (t, J_{C-F} = 22.0 Hz), 130.9 (t, J_{C-F} = 1.9 Hz), 125.7 (t, J_{C-F} = 6.0 Hz), 114.9 (t, J_{C-F} = 237.1 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ -110.5 (d, 2F, J_{F-H} = 55.4 Hz).

4-(Difluoromethyl)-1,1'-biphenyl (3b)
White solid. NMR yield (93%) was determined by using BTF as an internal standard. The residue was purified by silica-gel column chromatography (hexane only) to afford the compound (68.6 mg, 84% yield). The product is known compound and the following data are identical to those given in corresponding literature.[7c] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70-7.67 (m, 2H), 7.62-7.58 (m, 4H), 7.50-7.45 (m, 2H), 7.42-7.38 (m, 1H), 6.71 (t, J_{H-F} = 56.5 Hz); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 143.9 (t, J_{C-F} = 1.8 Hz), 140.3, 133.3 (t, J_{C-F} = 22.2 Hz), 129.1, 128.0, 127.6, 127.4, 126.2 (t, J_{C-F} = 6.0 Hz), 114.9 (t, J_{C-F} = 236.9 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ -110.3 (d, 2F, J_{F-H} = 56.9 Hz).

3-(Difluoromethyl)-1,1'-biphenyl (3c)
Colorless liquid. NMR yield (85%) was determined by using BTF as an internal standard. The residue was purified by silica-gel column chromatography (2% EtOAc in hexane) to afford the compound (66.2 mg, 81% yield). The product is known compound and the following data are identical to those given in corresponding literature.[9a] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75-7.71 (m, 2H), 7.64-7.57 (m, 2H), 7.55-7.46 (m, 4H), 7.43-7.38 (m, 1H), 6.73 (t, J_{H-F} = 56.4 Hz); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 142.0, 140.3, 135.0 (t, J_{C-F} = 22.2 Hz), 129.6 (t, J_{C-F} = 2.1 Hz), 129.3, 129.0, 127.9, 127.3, 124.5 (t, J_{C-F} = 3.2 Hz), 124.4 (t, J_{C-F} = 3.4 Hz), 114.9 (t, J_{C-F} = 237.4 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ -110.5 (d, 2F, J_{F-H} = 55.2 Hz).

1- (Difluoromethyl)naphthalene (3d)
Colorless liquid. NMR yield (85%) was determined by using BTF as an internal standard. The residue was purified by silica-gel column chromatography (1% EtOAc in hexane) to afford the compound (58.4 mg, 82% yield). The product is known compound and the following data are identical to those given in corresponding literature.[9a] ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20 (d, 1H, J = 8.0 Hz), 7.99-7.91 (m, 2H), 7.71 (d, 1H, J = 7.0 Hz), 7.65-7.59 (m, 2H), 7.57-7.49 (m, 1H), 7.15 (t, J_{H-F} = 55.2 Hz); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 133.9, 131.6 (t, J_{C-F} = 1.9 Hz), 129.8 (t, J_{C-F} = 2.5 Hz), 129.7 (t, J_{C-F} = 20.7 Hz), 128.9, 127.3, 126.5, 124.9 (t, J_{C-F} = 7.0 Hz), 124.8, 123.7, 115.6 (t, J_{C-F} = 237.0 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ -110.8 (d, 2F, J_{F-H} = 55.3 Hz).

2- (Difluoromethyl)naphthalene (3e)
White solid. NMR yield (94%) was determined by using BTF as an internal standard. The residue was purified by silica-gel column chromatography (1% EtOAc in hexane) to afford the compound (64.1 mg, 90% yield). The product is known compound and the following data are identical to those given in corresponding literature.[9a] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99-7.88 (m, 4H), 7.62-7.53 (m, 3H), 6.82 (t, J_{H-F} = 56.3 Hz); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 134.4 (t, J_{C-F} = 1.7 Hz), 132.7, 131.7 (t, J_{C-F} = 22.2 Hz), 129.0, 128.7, 128.0, 127.5, 126.9, 126.0 (t, J_{C-F} = 7.5 Hz), 122.1 (t, J_{C-F} = 4.7 Hz), 115.2 (t, J_{C-F} = 236.9 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ -109.8 (d, 2F, J_{F-H} = 55.3 Hz).

9-(Difluoromethyl)phenanthrene (3f)
White solid. NMR yield (65%) was determined by using BTF as an internal standard. The residue was purified by silica-gel column chromatography (hexane only) to afford the compound (50.2 mg, 55% yield). The product is known compound and the following data are identical to those given in corresponding literature.[9a] ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.71 (dd, 2H, J = 9.0 Hz, J = 1.8 Hz), 8.25-8.22 (m, 1H), 7.97-7.92 (m, 2H), 7.76-7.62 (m, 4H), 7.16 (t, 1H, J = 55.0 Hz); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 131.5, 130.9, 130.2, 129.6, 128.4, 128.0 (t, J_{C-F} = 6.0 Hz), 127,8, 127.3, 127.25, 127.23, 126.9 (t, J_{C-F} = 9.3 Hz), 124.6 (t, J_{C-F} = 2.1 Hz), 123.4, 122.8, 115.8 (t, J_{C-F} = 237.1 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ -111.7 (d, 2F, J_{F-H} = 54.9 Hz).

2-(Difluoromethyl)-9,9-dimethyl-9H-fluorene (3g)
White solid. NMR yield (77%) was determined by using BTF as an internal standard. The residue was purified by silica-gel column chromatography (hexane only) to afford the compound (71.3 mg, 73% yield). The product is known compound and the following data are identical to those given in corresponding literature.[9b] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80-7.77 (m, 2H), 7.59 (s, 1H), 7.50-7.45 (m, 2H), 7.40-7.35 (m, 2H), 6.73 (t, J_{H-F} = 56.7 Hz), 1.52 (s, 6H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 154.2, 154.2, 141.9 (t, J_{C-F} = 2.2 Hz), 138.3, 133.2 (t, J_{C-F} = 21.9 Hz), 128.2, 127.3, 124.9 (t, J_{C-F} = 6.3 Hz), 122.9, 120.6, 120.2, 120.0 (t, J_{C-F} = 5.9 Hz), 115.3 (t, J_{C-F} = 236.9 Hz), 47.2, 27.1; ^{19}F NMR (282 MHz, $CDCl_3$) δ -109.0 (d, 2F, J_{F-H} = 55.2 Hz).

1-(Difluoromethyl)pyrene (3h)
White solid. NMR yield (88%) was determined by using BTF as an internal standard. The residue was purified by silica-gel column chromatography (hexane only) to afford the compound

(69.6 mg, 69% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.37 (t, 1H, J = 9.3 Hz), 8.25-8.17 (m, 5H), 8.14-8.11 (m, 1H), 8.08-8.03 (m, 2H), 7.46 (t, 1H, J_{H-F} = 55.4 Hz); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 133.2 (t, J_{C-F} = 1.7 Hz), 131.2, 131.0, 130.5, 129.1, 129.0, 128.6 (t, J_{C-F} = 3.8 Hz), 127.3, 126.5, 126.2, 126.1, 124.5, 123.7 (t, J_{C-F} = 7.8 Hz), 122.4, 115.5 (t, J_{C-F} = 236.8 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ -108.8 (d, 2F, J_{F-H} = 55.6 Hz). HRMS (APCI-TOF) $[M+H_3O]^+$ calcd for $C_{17}H_{13}F_2O$: 271.0935; found: 271.0939.

1-(Difluoromethyl)-4-methoxybenzene (3i)

Colorless liquid. NMR yield (83%) was determined by using BTF as an internal standard. The residue was purified by silica-gel column chromatography (2% Et_2O in pentane) to afford the compound (32.9 mg, 52% yield). The product is known compound and the following data are identical to those given in corresponding literature.[7c] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (d, 2H, J = 8.4 Hz), 6.96 (d, 2H, 8.6 Hz), 6.60 (t, 1H, J_{H-F} = 56.7 Hz), 3.84 (s, 3H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 161.5, 127.3 (t, J_{C-F} = 5.9 Hz), 126.9 (t, J_{C-F} = 22.6 Hz), 115.0 (t, J_{C-F} = 235.8 Hz), 114.1, 55.5; ^{19}F NMR (282 MHz, $CDCl_3$) δ -108.2 (d, 2F, J_{F-H} = 56.1 Hz).

1-(Difluoromethyl)-4-phenoxybenzene (3j)

Colorless liquid. NMR yield (91%) was determined by using BTF as an internal standard. The residue was purified by silica-gel column chromatography (3% EtOAc in haxane) to afford the compound (74.9 mg, 85% yield). The product is known compound and the following data are identical to those given in corresponding literature.[9a] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (d, 2H, J = 8.5 Hz), 7.42-7.37 (m, 2H), 7.18 (t, 1H, 7.4 Hz), 7.08, 7.05 (m, 4H), 6.64 (t, 1H, J_{H-F} = 56.6 Hz); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 159.7 (t, J_{C-F} = 2.1 Hz), 156.3, 130.1, 129.0 (t, J_{C-F} = 22.5 Hz), 127.5 (t, J_{C-F} = 5.9 Hz), 124.2, 119.8, 118.4, 114.7 (t, J_{C-F} = 236.5 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ -109.0 (d, 2F J_{F-H} = 55.4 Hz).

[4-(Difluoromethyl)phenyl](methyl)sulfane (3k)

Yellow liquid. NMR yield (63%) was determined by using BTF as an internal standard. The residue was purified by silica-gel column chromatography (2% EtOAc in hexane only) to afford the compound (40.4 mg, 58% yield). The product is known compound and the following data are identical to those given in corresponding literature.[26] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 (d, 2H, J = 8.3 Hz), 7.29 (d, 2H, 8.4 Hz), 6.61 (t, 1H, J_{H-F} = 56.5 Hz), 2.50 (s, 3H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 142.3 (t, J_{C-F} = 2.1 Hz), 130.9 (t, J_{C-F} = 22.4 Hz), 126.1 (t, J_{C-F} = 5.3 Hz), 114.7 (t, J_{C-F} = 236.7 Hz), 15.3; ^{19}F NMR (282 MHz, $CDCl_3$) δ -109.9 (d, 2F, J_{F-H} = 55.2 Hz).

1-(*tert*-Butyl)-4-(Difluoromethyl)benzene (3l)

Colorless liquid. NMR yield (78%) was determined by using BTF as an internal standard. The residue was purified by silica-gel column chromatography (pentane only) to afford the compound (48.6 mg, 66% yield). The product is known compound and the following data are identical to those given in corresponding literature.[7c] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (m, 4H, J = 8.8 Hz), 6.63 (t, 1H, J_{H-F} = 56.7 Hz), 1.34 (s, 9H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 154.1 (t, J_{C-F} = 2.1 Hz), 131.7 (t, J_{C-F} = 22.4 Hz), 125.5 (t, J_{C-F} = 5.9 Hz), 125.4 115.0 (t, J_{C-F} = 236.6 Hz), 35.0, 31.4; ^{19}F NMR (282 MHz, $CDCl_3$) δ -109.9 (d, 2F, J_{F-H} = 55.7 Hz).

2-(Difluoromethyl)-6-methoxynaphthalene (3m)

White solid. NMR yield (93%) was determined by using BTF as an internal standard. The residue was purified by silica-gel column chromatography (3% Et_2O in hexane) to afford the compound (68.3 mg, 82% yield). The product is known compound and the following data are identical to those given in corresponding literature.[12a] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.80 (dd, 2H, J = 10.8 Hz, 8.0 Hz), 7.57 (d, 1H, J = 8.4 Hz), 7.24-7.21 (m, 1H), 7.20-7.16 (m, 1H), 6.78 (t, 1H, J_{H-F} = 56.5 Hz), 3.94 (s, 3H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 158.9, 135.9 (t, J_{C-F} = 1.2 Hz), 130.1, 129.5 (t, J_{C-F} = 22.2 Hz), 128.1, 127.7, 125.8 (t, J_{C-F} = 7.4 Hz), 122.7 (t, J_{C-F} = 4.7 Hz), 119.8, 115.4 (t, J_{C-F} = 236.6 Hz), 105.9, 55.5; ^{19}F NMR (282 MHz, $CDCl_3$) δ -108.9 (d, 2F, J_{F-H} = 55.6 Hz).

1-(Difluoromethyl)-4-(trifluoromethyl)benzene (3n)

Colorless liquid. NMR yield (57%) was determined by using trifluoromethoxybenzene (Ph-OCF_3) as an internal standard. The residue was purified by silica-gel column chromatography (pentane only) to afford the compound (12.6 mg, 16% yield). The product is known compound and the following data are identical to those given in corresponding literature.[27] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (d, 2H, J = 8.2 Hz), 7.65 (d, 2H, 8.0 Hz), 6.71 (t, 1H, J_{H-F} = 56.0 Hz); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 137.8 (t, J_{C-F} = 22.4 Hz), 132.8 (q, J_{C-F} = 32.6 Hz), 126.1 (t, J_{C-F} = 6.0 Hz), 125.8 (q, J_{C-F} = 3.8 Hz), 123.6 (q, J_{C-F} = 270.8 Hz), 113.7 (t, J_{C-F} = 238.5 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ -63.1 (s, 3F), -112.4 (d, 2F, J_{F-H} = 55.4 Hz).

4-(Difluoromethyl)benzonitrile (3o)

Orange liquid. NMR yield (45%) was determined by using BTF as an internal standard. The residue was purified by silica-gel column chromatography (3% EtOAc in hexane) to afford the compound (22.3 mg, 36% yield). The product is known compound and the following data are identical to those given in corresponding literature.[7c] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, 2H, J = 8.1 Hz), 7.66 (d, 2H, J = 8.6 Hz), 6.71 (t, 1H, J_{H-F} = 55.8 Hz); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 138.6 (t, J_{C-F} = 22.8 Hz), 132.6, 126.4 (t, J_{C-F} = 6.0 Hz), 117.9, 114.8, 113.3 (t, J_{C-F} = 239.4 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ -113.1 (d, 2F, J_{F-H} = 55.6 Hz).

Ethyl 4-(Difluoromethyl)benzoate (3p)

Colorless liquid. NMR yield (62%) was determined by using BTF as an internal standard. The residue was purified by silica-gel column chromatography (3% EtOAc in hexane) to afford the compound (44.0 mg, 55% yield). The product is known compound and the following data are identical to those given in corresponding literature.[7c] ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13 (d, 2H, J = 8.0 Hz), 7.58 (d, 2H, J = 8.2 Hz), 6.69 (t, 1H, J_{H-F} = 56.1 Hz), 4.40 (q, 2H, J = 7.1 Hz), 1.41 (t, 3H, J = 7.1 Hz); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 165.9, 138.5 (t, J_{C-F} = 22.9 Hz), 132.8 (t, J_{C-F} = 2.0 Hz), 130.0, 125.7 (t, J_{C-F} = 6.0 Hz), 114.2 (t, J_{C-F} = 238.2 Hz), 61.5, 14.4; ^{19}F NMR (282 MHz, $CDCl_3$) δ -112.2 (d, 2F, J_{F-H} = 56.7 Hz).

1-(Difluoromethyl)-4-fluoronaphthalene (3q)

White solid. NMR yield (61%) was determined by using BTF as an internal standard. The residue was purified by silica-gel column chromatography (3% Et_2O in hexane) to afford the compound (43.9 mg, 56% yield). 1H NMR (300 MHz, CDCl3) δ 8.21 (d, 2H, J = 7.7. Hz), 7.70-7.62 (m, 4H), 7.18 (t, 1H, J = 8.6 Hz), 7.10 (t, 1H, J_{H-F} = 55.1 Hz); ^{13}C {^{1}H} NMR (75 MHz,

$CDCl_3$) δ 160.6 (dt, J_{C-F} = 254.7 Hz, 2.0 Hz), 131.4 (dt, J_{C-F} = 25.6 Hz, 2.4 Hz), 128.3, 126.9 (d, J_{C-F} = 1.9 Hz), 125.8 (td, J_{C-F} = 17.4 Hz, 4.3 Hz), 125.5 (dt, J_{C-F} = 9.3 Hz, 9.0 Hz), 124.2 (d, J_{C-F} = 16.4 Hz), 123.7 (dt, J_{C-F} = 2.5 Hz, 1.7 Hz), 121.4 (d, J_{C-F} = 5.9 Hz), 115.2 (t, J_{C-F} = 236.8 Hz), 108.4 (d, J_{C-F} = 20.8 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ -110.1 (d, 2F, J_{F-H} = 55.0 Hz), -117.9 (s, 1F). HRMS (APCI-TOF) $[M-H]^-$ calcd for $C_{11}H_6F_3$: 195.0422; found: 195.0429.

1-(Difluoromethyl)-3,5-dimethoxybenzene (3r)
Colorless liquid. NMR yield (85%) was determined by using BTF as an internal standard. The residue was purified by silica-gel column chromatography (5% Et_2O in hexane) to afford the compound (57.9 mg, 77% yield). The product is known compound and the following data are identical to those given in corresponding literature.[12b] ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.64 (s, 2H), 6.56 (t, 1H, J_{H-F} = 56.5 Hz), 6.54 (s, 1H), 3.82 (s, 6H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 161.2, 136.5 (t, J_{C-F} = 22.3 Hz), 114.6 (t, J_{C-F} = 237.8 Hz), 103.5 (t, J_{C-F} = 6.3 Hz), 102.8 (t, J_{C-F} = 1.9 Hz), 55.6; ^{19}F NMR (282 MHz, $CDCl_3$) δ -110.8 (d, 2F, J_{F-H} = 55.5 Hz).

Ethyl 3-(Difluoromethyl)benzoate (3s)
Colorless liquid. NMR yield (88%) was determined by using BTF as an internal standard. The residue was purified by silica-gel column chromatography (3% EtOAc in hexane) to afford the compound (64.1 mg, 80% yield). The product is known compound and the following data are identical to those given in corresponding literature.[9a] ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 (d, 2H, J = 9.7 Hz), 7.70 (d, 1H, J = 9.2 Hz), 7.54 (t, 1H, J = 7.7 Hz), 6.69 (t, 1H, J_{H-F} = 56.2 Hz), 4.40 (q, 2H, J = 7.1 Hz), 1.40 (t, 3H, J = 7.1 Hz); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 165.8, 134.8 (t, J_{C-F} = 22.8 Hz), 131.9 (t, J_{C-F} = 2.0 Hz), 131.2, 129.8 (t, J_{C-F} = 5.8 Hz), 129.0, 127.0 (t, J_{C-F} = 6.3 Hz), 114.3 (t, J_{C-F} = 238.0 Hz), 61.5, 14.4; ^{19}F NMR (282 MHz, $CDCl_3$) δ -111.1 (d, 2F, J_{F-H} = 56.5 Hz).

5-(Difluoromethyl)benzo[d][1,3]dioxole (3t)
Colorless liquid. NMR yield (73%) was determined by using BTF as an internal standard. The residue was purified by silica-gel column chromatography (2% Et_2O in hexane) to afford the compound (45.5 mg, 66% yield). The product is known compound and the following data are identical to those given in corresponding literature.[9b] ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.97 (d, 2H, J = 7.1 Hz), 6.85 (d, 1H, J = 8.5 Hz), 6.54 (t, 1H, J_{H-F} = 56.6 Hz), 6.02 (s, 2H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 149.7 (t, J_{C-F} = 1.8 Hz), 148.2, 128.4 (t, J_{C-F} = 22.6 Hz), 120.3 (t, J_{C-F} = 7.2 Hz), 114.8 (t, J_{C-F} = 236.6 Hz), 108.4, 105.9 (t, J_{C-F} = 5.5 Hz), 101.7; ^{19}F NMR (282 MHz, $CDCl_3$) δ -107.9 (d, 2F, J_{F-H} = 55.5 Hz).

1-(Difluoromethyl)-2-methylbenzene (3u)
Colorless liquid. NMR yield (84%) was determined by using BTF as an internal standard. The residue was purified by silica-gel column chromatography (pentane only) to afford the compound (18.7 mg, 33% yield). The product is known compound and the following data are identical to those given in corresponding literature.[5a] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (d, 1H, J = 7.4 Hz), 7.30-7.25 (m, 1H), 7.20-7.13 (m, 2H), 6.67 (t, 1H, J_{H-F} = 55.4 Hz), 2.35 (s, 3H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 136.4 (t, J_{C-F} = 6.0 Hz), 132.3 (t, J_{C-F} = 20.6 Hz), 131.2, 130.7 (t, J_{C-F} = 1.9 Hz), 126.1, 125.9 (t, J_{C-F} = 7.5 Hz), 114.6 (t, J_{C-F} = 236.4 Hz), 18.6; ^{19}F NMR (282 MHz, $CDCl_3$) δ -113.1 (d, 2F, J_{F-H} = 55.4 Hz).

9-[4-(Difluoromethyl)phenyl]-9H-carbazole (3v)
White solid. NMR yield (88%) was determined by using BTF as an internal standard. The residue was purified by silica-gel column chromatography (5% EtOAc in hexane) to afford the compound (92.4 mg, 79% yield). The product is known compound and the following data are identical to those given in corresponding literature.[28] ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 (d, 2H, J = 7.7 Hz), 7.78 (d, 2H, J = 8.3 Hz), 7.70 (d, 2H, J = 8.4 Hz), 7.45-7.43 (m, 4H), 7.35-7.30 (m, 2H), 6.79 (t, J_{H-F} = 56.3 Hz); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 140.6, 140.2 (t, J_{C-F} = 2.1 Hz), 133.3 (t, J_{C-F} = 22.6 Hz), 127.4 (t, J_{C-F} = 6.0 Hz), 127.3, 126.3, 123.7, 120.6, 120.5, 114.4 (t, J_{C-F} = 237.5 Hz), 109.8; ^{19}F NMR (282 MHz, $CDCl_3$) δ -110.4 (d, 2F, J_{F-H} = 55.2 Hz).

2-[4-(Difluoromethyl)phenyl]pyridine (3w)
White solid. NMR yield (63%) was determined by using BTF as an internal standard. The residue was purified by silica-gel column chromatography (20% EtOAc in hexane) to afford the compound (43.5 mg, 53% yield). The product is known compound and the following data are identical to those given in corresponding literature.[12a] ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.71-8.69 (m, 1H), 8.13 (d, 2H, J = 7.9 Hz), 7.82-7.79 (m, 2H), 7.63 (d, 2H, J = 7.6 Hz), 7.32-7.27 (m, 1H), 6.74 (t, J_{H-F} = 56.4 Hz); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 156.3, 150.1, 142.1 (t, J_{C-F} = 1.9 Hz), 137.3, 135.0 (t, J_{C-F} = 22.0 Hz), 127.5, 126.3 (t, J_{C-F} = 6.1 Hz), 123.2, 121.0, 115.2 (t, J_{C-F} = 236.6 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ -110.0 (d, 2F, J_{F-H} = 55.2 Hz).

2-[4-(Difluoromethyl)phenyl]thiophene (3x)
Yellow solid. NMR yield (73%) was determined by using BTF as an internal standard. The residue was purified by silica-gel column chromatography (hexane only) to afford the compound (49.7 mg, 59% yield). The product is known compound and the following data are identical to those given in corresponding literature.[12a] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, 2H, J = 8.3 Hz), 7.53 (d, 2H, J = 8.2 Hz), 7.38-7.34 (m, 2H), 6.67 (t, 1H, J_{H-F} = 56.5 Hz); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 143.2, 136.9 (t, J_{C-F} = 2.3 Hz), 133.3 (t, J_{C-F} = 22.3 Hz), 128.3, 126.3 (t, J_{C-F} = 6.1 Hz), 126.1, 125.9, 124.2, 114.7 (t, J_{C-F} = 237.0 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ -110.5 (d, 2F, J_{F-H} = 58.1 Hz).

Radical Clock Experiment[11]

In an argon-filled glovebox, $Fe(acac)_3$ (3.5 mg, 0.0005 mmol, 2.5 mol%) was weighed and added to 10 mL test tube. After the tube was sealed with a septum, THF (2 mL) was added to a solution and this was added difluoroiodomethane in THF (1.2-1.8 M, 110-160 μL, 0.20 mmol) and diallyl ether (50 μL, 0.4 mmol) at room temperature. The solution was cooled to -20 ℃ then, phenylmagnesiumbromide (1.0 M in THF, 0.4 mL, 0.4 mmol) was dropwised over 30 min. The reaction mixture was monitored by ^{19}F NMR analysis using BTF as an internal standard. The ring-closing product **5** (-115.9 ppm) was formed in 5% yield and decrease in yield of product was observed.

Radical Capture Experiment[18]

In an argon-filled glovebox, $Fe(acac)_3$ (3.5 mg, 0.001 mmol, 2.5 mol %) and 2,2,6,6-tetramethylpiperidine 1-oxyl were added to 10 mL test tube. After the tube was sealed with a

septum, THF (4 mL) was added. To this solution was added difluoroiodomethane **2** in THF (1.2-1.8 M, 220-330 μL, 0.40 mmol) at room temperature. The solution was cooled to -20 ℃ then, phenylmagnesiumbromide **1a** (ca. 0.5 M in THF, 1.6 mL, 0.8 mmol) was added dropwise over 30 min. After warmed up to at room temperature, NMR yield was determined by using benzotrifluoride (BTF) as an internal standard. The coupling product **3a** was not obtained and TEMPO-CF_2H **5** (-80.7 ppm) was formed in 33% yield.

ASSOCIATED CONTENT

Supporting Information

Copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

* E-mail for K. M.: mikami.k.ab@m.titech.ac.jp.

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