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Silver-mediated C-H Difluoromethylation of Arenes

Jialiang Li,[a] Wen Wan, *[a] Guobin Ma,[a] Yunrong Chen,[a] Qingyang Hu,[a] Kai Kang,[a] Haizhen Jiang,[a] Jian Hao, *[a], [b]

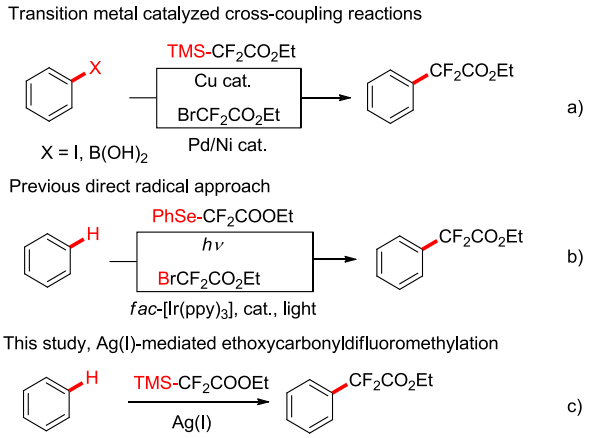
Abstract: The first Ag(I)-mediated C-H ethoxycarbonyl difluoromethylation with $TMSCF_2COOEt$ has been developed. The radical difluoromethylation proceeds smoothly to give the difluoromethylated arenes in moderate to high yield with a Friedel–Crafts-type regioselectivity. Mechanistic investigation indicates that the innate C−H difluoromethylation proceeds through an electrophilic radical-type pathway.

Introduction

As fluoroalkyl groups can endow organic molecules with novel and useful physical and biological properties,[1] aromatic compounds having functionalized CF_2 moiety, such as ethoxycarbonyldifluoromethyl (CF_2CO_2Et) group, have attracted particular attention due to its unique difluoromethylene group which can act as a bio-isostere for an ethereal oxygen atom,[2] as well as its nature as a powerful synthetic intermediate for the huge possibility of post-functionalization to other functional groups.[3] The general and convenient procedures to these difluorinated compounds are synthesized through deoxyfluorination from oxoarylacetate with DAST, PPHF, SF_4, or XeF_2.[4] However, these difluorination processes are unsuitable for their practical use due to the harsh conditions, poor functional group tolerance, toxic and explosive nature of these fluorinating reagents.

In contrast to the significant achievements that have been made in the perfluoroalkylation, first of all, the trifluoromethylationstudies,[5] efficient and general introduction of functionalized difluorinated moieties remains underexplored.[6] The CF_2CO_2Et moiety is extremely appealing among the difluorinated substituents, because it can be transformed into a variety of other difluoromethylene containing functional groups. Over the past several years, the efficient ways to access to such key difluorinated arenes have intensively focused on the transition-metal-mediated or catalyzed cross-coupling reaction with organometallic derivatives or halogenated fluorinated species (Scheme 1a).[3c, 7] Until recently, the radical C-H functionalization has attracted considerable attention, since it allows the direct functionalization of molecules without prior functional group manipulation. For instance, Fuchigami reported a photochemical difluoromethylation of arenes in the presence of difluorophenylselenoacetate. Yamakawa described a difluoromethylation of electron-rich heteroaromatic compounds and aniline derivatives using Fenton reagent. Cho presented a strategy for the difluoromethylation of aromatics employing *fac*-$[Ir(ppy)_3]$ as the photoredox catalyst under visible light irradiation (Scheme 1b).[8] These free radical processes are considered to be an industrially promising procedure for the direct introduction of CF_2CO_2Et group into arenes, because it precludes the requirement for pre-functionalization of the starting materials. Despite these important advances, the current strategies for the direct introduction of ethoxycarbonyl difluoromethyl group are still suffering from one or more limitations, such as the high toxicity of selenium, or using expensive noble metals or photocatalyst, a limited substrate scope in electron-rich arenes. It is still desirable to develop more efficient C-H bond ethoxycarbonyl difluoromethylation of arenes to address these issues.

Scheme 1. Strategies for silver (I)-mediated C-H difluoromethylation of arenes



We are interested in the possibility of addressing some of these limitations by using metals Cu or Ag,[9] as there are a number of reports describing the reactivity of $CuCF_2R$ or $AgCF_2R$ complexes.[10] Recently, we successfully realized the radical difluoromethylation of various unactivated alkenes using $TMSCF_2COOEt$ as difluoromethylating reagent and $PhI(OAc)_2$ as oxidant in the presence of AgOTf,[11] which thereby suggested the opportunities for the direct difluoromethylation on arenes. Herein, we described the Ag(I)-mediated introduction of CF_2COOEt moiety into arenes by means of direct C−H functionalization through radical process (Scheme 1c).

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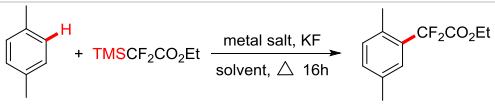
Results and Discussion

On the basis of our previous work and relative works on silver-mediated difluoromethylation of unactivated alkenes, we began our investigation at the point that the CF_2COOEt radical could be generated from $AgCF_2COOEt$ intermediate. This Ag-mediated direct C-H difluoromethylation was optimized using *p*-xylene **1a** as a model substrate (Table 1). Considering the expensive difluoromethylating reagent ($TMSCF_2COOEt$), the excessive amount of cheap *p*-xylene was applied in this study on optimization of difluoromethylation reaction. The excessive *p*-xylene could be recovered after the reaction was completed. To our delight, treatment of **1a** with $TMSCF_2COOEt$ **2a** could afford the desired product **3a** with 5% yield detected by ^{19}F NMR analysis, in the presence of AgOAc (entry 4), and KF as base to activate the $TMSCF_2COOEt$. Replacement of silver salt with copper slats, such as CuI, CuTc and $CuBr_2$, resulted in the failure of difluoromethylation of this reaction (entries 1-3). Though the use of solvents, such as CH_3CN, DMF, NMP, THF, DMSO did not give acceptable results (entries 4-8), 1,2-dichloroethane (DCE) was suitable for this transformation (entry 9). Further examination of different silver slats indicated that AgOTf is the most reactive silver source and dramatically increased the yield to 56% (entries 10-12). High loading of AgOTf and the base of KF notably improved the yield to 91% (entry 14). However, the yield of reaction was significantly reduced down to 42% when the usage of $TMSCF_2COOEt$ increased (entry 15). Control experiments demonstrated that no desired product was generated in the absence of a base or silvers alt.

Having established these optimized conditions (Table 1, entry 14), we investigated the scope of different non-prefunctionalized aromatics. As shown in Table 2, the reactions of arenes bearing electron-donating alkyl or alkoxy substituents afforded good to high yield. In general, the difluoromethylation transformations proceeded with a modest preference for difluoromethylation at C-H sites *ortho* and *para* to the alkyl groups **3c**. The alkoxylated arenes could give good yields with higher regioselectivity at the *ortho* to the electron-donating alkoxy groups **3f**-**m**. The difluoromethylation of naphthalene **1n** and anthracene **1o** proceeded well with high regioselectivity for the 1- and 9-position, respectively. The observed regioselectivity is similar to that observed for a Friedel-Crafts-type reaction. The site selectivity of these reactions was consistent with that anticipated for a radical aromatic substitution pathway.[12] Notably, a range of functional groups, such as chloride, bromide, iodide and fluoride, as well as methoxy or ester groups (**1f**-**m**), are well-tolerated, which make these compounds interesting for further functionalization, such as cross-coupling reactions. Some of the difluoromethylation of alkylated or alkoxylated arenes provided unseparable iso-difluoromethylated arenes (**3c**, **3f**). The isomer ratios were determined by ^{19}F NMR analysis and the chemical structures of these unseparable isomers by flash chromatography were further studied by detailed ^{1}H NMR and GC-MS analysis (see the Supporting Information). The difluoromethylation of some substrates bearing symmetric substituents, such as *p*-xylene **1a**, benzne **1b**, mesitylene **1d**, 1,2,4,5-tetramethylbenzene **1e**, 1,4-dimethoxybenzene **1g**, 1,3,5-trimethoxybenzene **1h**, gave the solo products in good to high yield with excellent regioselectivity. The hereoaromatics like thiophene was a good substrate for C-H difluoromethylation, affording the α-difluoromethylation as the main product 3p. In the case of 1,3,5-triisopropylbenzene, trace of the desired difluoromethylated product was obtained, due to the highly steric hindrance of isopropyl substituents.

Table 1. Optimization of difluoromethylation reaction [a]



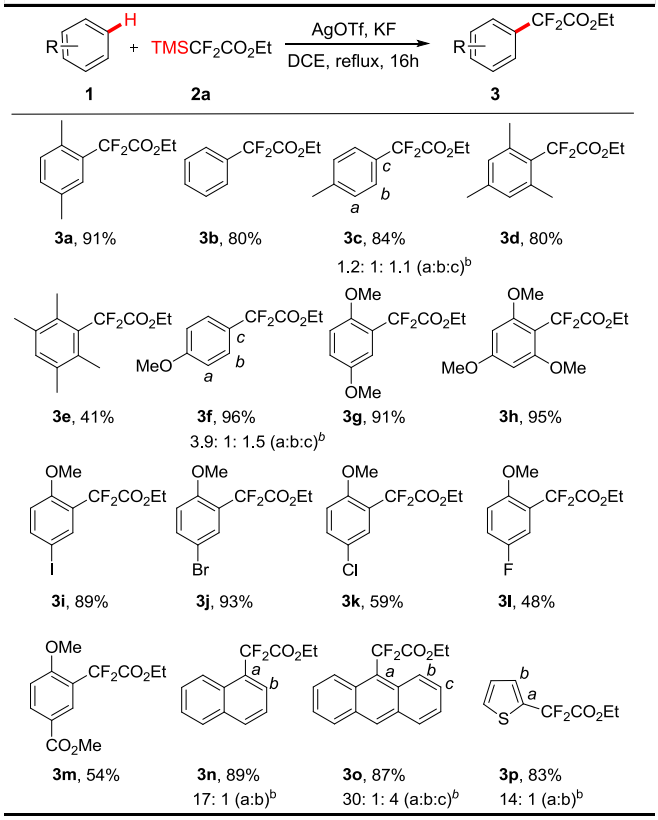
1a 2a 3a

Entry	Metal Salt	Metal salt/KF/**2a** (equiv.)	Solvent	Temp.	Yield (%)[b]
1	CuI	1:2:1	CH_3CN	80	0
2	CuTc	1:2:1	CH_3CN	80	0
3	$CuBr_2$	1:2:1	CH_3CN	80	0
4	AgOAc	2:2:1	CH_3CN	80	5
5	AgOAc	2:2:1	DMF	80	3
6	AgOAc	2:2:1	NMP	80	2
7	AgOAc	2:2:1	DMSO	80	trace
8	AgOAc	2:2:1	THF	60	8
9	AgOAc	2:2:1	DCE	80	13
10	AgF	2:2:1	DCE	80	38
11	$AgNO_3$	2:2:1	DCE	85	31
12	AgOTf	2:2:1	DCE	85	56
13	AgOTf	3:3:1	DCE	85	78
14	AgOTf	4:4:1	DCE	85	91
15[c]	AgOTf	4:4:3	DCE	85	42

[a] General conditions: *p*-xylene (10 equiv), $TMSCF_2CO_2Et$ (1 equiv) for 16 hr. [b] Yields determined by ^{19}F NMR analysis of crude product using $PhCF_3$ as the internal standard. [c] Conditions: *p*-xylene (1 equiv), $TMSCF_2CO_2Et$ (3 equiv), AgOTf (4 equiv), KF (4 equiv).

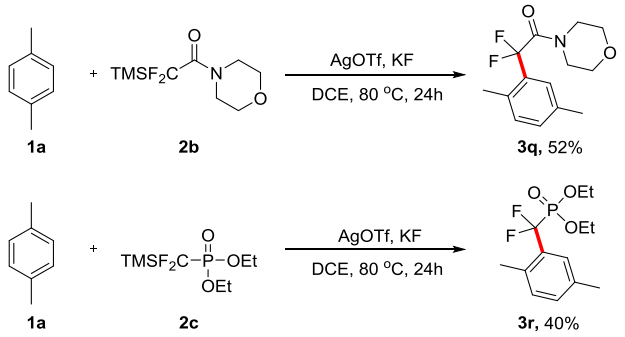
With these results in hand, we tried to expand the synthetic utility to other difluorinated TMS-sources by performing the direct introduction of difluoromethyl acetamide or difluoromethylphosphonate group into arenes. To our satisfactory, the difluoromethylated products **3q** and **3r** were obtained with moderate yield (Table 3). These results highlight the lower reactivity of difluorinated amide **2b** and phosphonate **2c** derivatives compared to the corresponding ester **2a**.

Table 2. Scope of difluoromethylation of N-arylacrylamides [a]



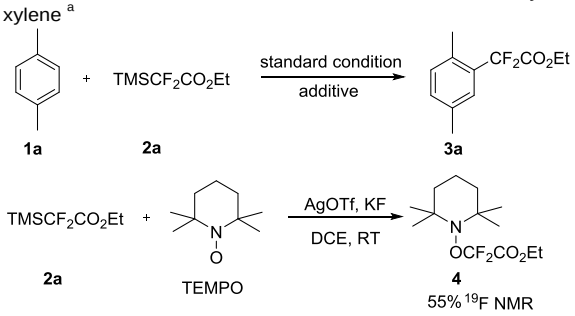
[a] Isolated yield. [b] Isomer ratio determined by ^{19}F NMR analysis.

Table 3. Introduction of difluoromethylacetamide or difluoromethyl-phosphonate group to arenes



To figure out whether the *in situ* generated difluoroemthylene radical (·CF_2COOEt) would be involved in the reaction, we attempted to perform the inhibition experiment of *p*-xylene **1a** in the presence of 1.0 equiv TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) as a radical scavenger, and a dramatic reduction in yield to only 8% of the desired product was observed. Applications of 1,4-dinitrobenzene (DNB) or hydroquinone to the reaction mixture of **1a** with $TMSCF_2COOEt$ under the standard reaction condition resulted in the complete suppression of the reaction. Thus, significant suppression of the formation of **3a** and further successful capture of ·CF_2COOEt by TEMPO provided the straightforward evidence of the ·CF_2COOEt radical formation, indicating that a ·CF_2COOEt radical species would act as an important role in the current reaction condition.

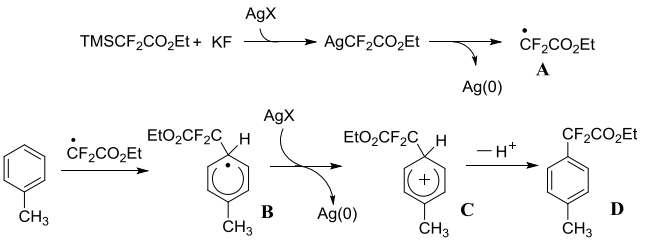
Table 4. Effect of additives on silver-mediated difluoromethylation of *p*-xylene [a]



Entry	Additive	Yield of **3a** [a]
1	none (ambient light)	91%
2	none (dark)	95%
3	1.0 equiv TEMPO	8%
4	1.0 equiv hydroquinone	trace
5[l]	1.0 equiv 1,4-dinitrobenzene	trace

[a] Yields determined by ^{19}F NMR spectroscopy with $PhCF_3$ as internal standard.

On the basis of this result in hand, a plausible working hypothesis is proposed for the radical reaction mechanism, as illustrated in Scheme 2. Initially, decomposition of the produced $AgCF_2COOEt$ affords the ·CF_2COOEt radical **A**. Subsequent addition of this radical species to the aromatic ring results in the formation of radical intermediate **B**. Radical **B** is then oxidized to cation **C** by Ag(I), followed by deprotonation to afford the final difluoromethylated product **D**. Owing to the electro-withdrawing nature of fluorine and ethoxycarbonyl group, the ·CF_2COOEt radical shows an electrophilic character. Therefore, this radical reaction presents an orientation similar to the electrophilic substitution of aromatic ring, which affords difluoromethylation at C-H sites *ortho* or *para* to the electron-donating alkyl or alkoxy groups, due to the favorable formation of more stable conjugated radical and carbon cation intermediates. This hypothesis might explain the Friedel–Crafts-type regioselectivity of this electrophilic radical difluoromethylation process.



Scheme 2. Proposed mechanism.

Conclusions

In conclusion, the first Ag(I)-mediated ethoxycarbonyl-difluoromethylation of arenes by simple C-H substitution employing inexpensive Ag(I) salt and $TMSCF_2COOEt$ as $^{\cdot}CF_2COOEt$ radical precursor is described, providing the CF_2COOEt substituted aromatic molecules in moderate to high yields. Since the functionalized CF_2 moiety in this work can be transformed into other difluoromethylene-containing functional groups, this reaction provides a new protocol for the direct introduction of difluoromethyl-containing ester, amide or phosphate into arenes. Additionally, primary mechanistic studies suggested a plausible electrophilic radical substitution process in this C-H difluoromethylation of arenes.

Experimental Section

^1H-, ^{13}C- and ^{19}F-NMR spectra were recorded in $CDCl_3$ on a Bruker AV-500 spectrometer. Chemical shifts for ^1H NMR spectra are reported in ppm relative to residual $CHCl_3$ as internal reference (δ 7.26 ppm for ^1H) downfield from TMS, chemical shifts for ^{13}C NMR spectra are reported in ppm relative to internal $CDCl_3$ (δ 77.16 ppm for ^{13}C), and chemical shifts for ^{19}F NMR spectra are reported in ppm downfield from internal fluoro trichloromethane ($CFCl_3$). Coupling constants (*J*) are given in Hertz (Hz). The terms m, s, d, t, q refer to multiplet, singlet, doublet, triplet, quartlet respectively; br refers to a broad signal. Infrared spectra (IR) were recorded on AVATAR 370 FT-IR spectrometer, absorbance frequencies are given at maximum of intensity in cm^{-1}. High resolution mass spectra (HRMS) and Mass spectra (MS) were recorded using an Electron impact (EI) or Electrospray ionization (ESI) techniques. GCMS analyses were performed on a Shimadzu GCMS-QP5000 gas chromatograph mass spectrometer. The products were separated on a 30 m length×0.25 mm i.d., RESTEK XTI-5 column coated with a 0.25 µm film. The GC oven temperature program was as follows: 30 ºC hold 10 min, ramp 20 ºC/min to 250 ºC, and hold for 3 min. Helium was employed as the carrier gas, with a constant column flow of 1.5 mL/min. The injector temperature was held constant at 250 ºC.

General Procedure of Silver-mediated Innate C-H Ethoxycarbonyldifluoromethylenation of Arenes

In a glove box, AgOTf (512 mg, 2 mmol, 4 equiv) and KF (116 mg, 2 mmol, 4 equiv) were weighed into a 4mL vial and dissolved in DCE (2mL). The aromatic substrate (10 equiv) and $TMSCF_2COOEt$ **2a** (98 mg, 0.5 mmol, 1equiv) were added. The vial was sealed with a Teflon-lined cap and removed from the glove box. The reaction was heated at 85 °C for 16 hr with exclusion of light. The resulting dark brown mixture was cooled to room temperature and diluted with DCE (10 mL). Then the reaction mixture was extracted with ethyl acetate and water. The combined organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography on silica gel to give the desired difluoromethylated arenes.

Ethyl 2-(2,5-dimethylphenyl)-2,2-difluoroacetate (3a)

Colorless liquid (103.7 mg, 91%). ^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.39 (s, 1H), 7.17 (d, *J*=7.8, 1H), 7.11 (d, *J*=7.8, 1H), 4.32 (q, *J* = 7.1, 2H), 2.38 (s, 3H), 2.36 (s, 3H), 1.31 (t, *J* = 7.1, 3H); ^{19}F NMR (471 MHz, $CDCl_3$) δ ppm -101.25; ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 164.4 (t, *J* = 35.2), 135.6, 133.3 (t, *J* = 3.1), 131.9, 131.5, 130.9 (t, *J* = 23.1), 126.7 (t, *J* = 8.7), 114.4 (t, *J* = 251.6), 63.2 , 21.0, 19.2, 14.0; IR (KBr, cm^{-1}): ν_{max} = 2982, 2929, 1765, 1054, 1291, 1088, 1027, 817.

Ethyl 2,2-difluoro-2-phenylacetate (3b)

Colorless liquid (80.1 mg, 80%). ^1H NMR (500 MHz, $CDCl_3$) δ = 7.66 - 7.61 (m, 2H), 7.51 - 7.41 (m, 3H), 4.28 (q, *J*=7.1, 2H), 1.28 (t, *J*=7.1, 3H); ^{19}F NMR (471 MHz, $CDCl_3$) δ -103.77; ^{13}C NMR (126 MHz, $CDCl_3$) δ = 164.2 (t, *J*=35.3), 132.9 (t, *J*=25.5), 131.0, 128.7, 125.4 (t, *J* = 6.2), 113.5 (t, *J* = 251.8), 63.1 , 13.8. IR (KBr, cm^{-1}): ν_{max} = 2985, 2944, 1760, 1610, 1487, 1286, 1140, 1010, 782.

Ethyl 2,2-difluoro-2-(o (or m, or p)-tolyl) acetate (3c)

The isomers are inseparable by column chromagoraphy.^{19}F NMR analysis of the crude reaction mixture showed that the product was formed in 84% yield (89.9 mg) as a 1.2:1:1.1 mixture of the *ortho*, *meta* and *para*-difluoromethylated isomers. These products showed ^{19}F NMR signals in $CDCl_3$ at -101.24 ppm (*ortho* isomer), -103.66 ppm (*meta* isomer) and -103.32 ppm (*para* isomer). The identity of the products was further confirmed by GCMS analysis, where the product peaks were observed at 5.060 min 5.095 min and 5.235 min. The mass spectra *m/z* 214(M^+) of each products are identical with the proposed structures for each isomer.

Ethyl 2,2-difluoro-2-mesitylacetate (3d)

Colorless liquid (52.5 mg, 80%). ^1H NMR (500 MHz, $CDCl_3$) δ = 6.93 (s, 2H), 4.35 (q, *J* = 7.2, 2H), 2.52 (t, *J*=4.3, 6H), 2.33 (s, 3H), 1.36 (t, *J* = 7.2, 3H); ^{19}F NMR (471 MHz, $CDCl_3$) δ = -94.59; ^{13}C NMR (126 MHz, $CDCl_3$) δ = 164.5 (t, *J* = 35.5), 139.9, 137.5 (t, *J* = 3.3), 131.1, 126.9 (t, *J* = 22.5), 116.4 (t, *J* = 254.2) , 62.9 , 21.5 (t, *J* = 5.9), 20.6, 13.7.

Ethyl 2,2-difluoro-2-(2,3,5,6-tetramethylphenyl)acetate (3e)

Colorless liquid (96.9 mg, 41%). ^1H NMR (500 MHz, $CDCl_3$) δ = 7.14 (s, 1H), 4.42 (q, *J* = 7.1, 2H), 2.43 (t, *J* = 4.0, 6H), 2.33 (s, 6H), 1.42 (t, *J* = 7.1, 3H); ^{19}F NMR (471 MHz, $CDCl_3$) δ = -91.16 – -91.25 (m); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 164.7 (t, *J*=35.1), 135.1, 133.9, 133.8 (t, *J* = 3.2), 130.5 (t, *J* = 21.2), 116.5 (t, *J*=252.2), 62.9, 20.4, 16.8 (t, *J* = 6.7), 13.7; IR (KBr, cm^{-1}): ν_{max} =2982, 2942, 1765, 1468, 1286, 1142, 1084, 1011, 853, 769. HRMS m/z(ESI) calcd. for $C_{14}H_{19}F_2O_2$ (M + H) 257.1348, found 257.1346.

Ethyl 2,2-difluoro-2-methoxyphenyl)acetate (3f)

The isomers are inseparable by column chromagoraphy. ^{19}F NMR analysis of the crude reaction mixture showed that the product was formed in 96% yield (110.5 mg) as a 3.9 : 1 : 1.5 mixture of *ortho*, *meta* and *para*-difluoromethylated disomers. These products showed ^{19}F NMR signals in $CDCl_3$ at –102.59 ppm (a isomer), -103.71 ppm (b isomer) and -102.37 ppm (c isomer). The identity of the products was further confirmed by GCMS analysis, where the product peaks were observed at 7.560 min, 7.645 min and 8.475 min. The mass spectra *m/z* 230(M^+) of the products are identical with the proposed structures for each isomer.

Ethyl 2-(2,5-dimethoxyphenyl)-2,2-difluoroacetate (3g)

Colorless liquid (118.4 mg, 91%). ^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.18 (s, 1H), 6.96 (d, *J* = 9.0, 1H), 6.86 (d, *J* = 9.0, 1H), 4.34 - 4.27 (m, 2H), 3.77 (s, 3H), 3.74 (s, 3H), 1.28 (t, *J*=7.2, 3H); ^{19}F NMR (471 MHz, $CDCl_3$) δ ppm -102.38; ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 163.9 (t, *J* = 33.8), 153.6 , 150.8 (t, *J* = 5.1), 122.7 (t, *J* = 23.9), 117.4, 112.9, 112.1 (t, *J* = 248.4), 111.9 (t, *J* = 7.6), 62.7, 56.3, 55.8, 13.9; IR (KBr, cm^{-1}): ν_{max} = 2946, 2840, 1771, 1503, 1279, 1216, 1103, 1040, 818, 716.

Ethyl 2,2-difluoro-2-(2,4,6-trimethoxyphenyl)acetate (3h)

Colorless liquid (137.9 mg, 95%). ^1H NMR (500 MHz, $CDCl_3$) δ ppm 6.10 (s, 2H), 4.30 (q, *J* = 7.1, 2H), 3.79 (s, 3H), 3.76 (s, 6H), 1.30 (t, *J* = 7.1,

3H); ^{19}F NMR (471 MHz, $CDCl_3$) δ ppm -96.24; ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 164.8 (t, *J* = 33.3), 163.4, 160.2 (t, *J* = 2.6), 113.4 (t, *J* = 247.6), 102.6 (t, *J*=24.0), 91.4, 62.4, 56.1, 55.3, 14.0; IR (KBr, cm^{-1}): ν_{max} = 2987, 2928, 1772, 1593, 1466, 1233, 1159, 1091, 986, 837, 759.

Ethyl 2,2-difluoro-2-(5-iodo-2-methoxyphenyl)acetate (3i)

Colorless liquid (158.5 mg, 89%). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.88 (s, 1H), 7.72 (d, *J* = 8.2, 1H), 6.71 (d, *J* = 8.6, 1H), 4.31 (q, *J* = 7.1, 2H), 3.77 (s, 3H), 1.28 (t, *J* = 7.1, 3H); ^{19}F NMR (471 MHz, $CDCl_3$) δ ppm -103.08; ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 163.5 (t, *J* = 33.6), 156.6 (t, *J* = 4.9), 141.1, 135.1 (t, *J* = 7.9), 124.1 (t, *J* = 24.2), 113.7, 111.3 (t, *J* = 249.5), 82.3, 62.9, 55.9, 14.0; IR (KBr, cm^{-1}): ν_{max} = 2981, 2945, 1775, 1596, 1488, 1303, 1260, 1093, 1023, 813, 679. HRMS m/z(ESI) calcd. for $C_{11}H_{12}F_2IO_3$ (M+H) 356.9794, found 356.9791.

Ethyl 2-(5-bromo-2-methoxyphenyl)-2,2-difluoroacetate (3j)

Colorless liquid (143.7 mg, 93%). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.73 (d, *J* = 2.5, 1H), 7.54 (dd, *J* = 8.8, 2.2, 1H), 6.82 (d, *J* = 8.9, 1H), 4.31 (q, *J* = 7.1, 2H), 3.78 (s, 3H), 1.28 (t, *J* = 7.1, 3H); ^{19}F *NMR* (471 MHz, $CDCl_3$) δ ppm -103.11; ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 163.5(t, *J*=33.6), 155.9 (t, *J* = 4.8), 135.1, 129.4 (t, *J* = 7.9), 123.8 (t, *J* = 24.5), 113.2, 112.9, 111.5 (t, *J* = 249.5), 62.9, 56.1, 14.0; IR (KBr, cm^{-1}): ν_{max} = 2981, 2949, 1773, 1491, 1265, 1104, 1022, 812. HRMS m/z(ESI) calcd. for $C_{11}H_{12}BrF_2O_3$ (M + H) 308.9932, found 308.9935.

Ethyl 2-(5-chloro-2-methoxyphenyl)-2,2-difluoroacetate (3k)

Colorless liquid (78.1 mg, 59%). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.58 (d, *J* = 2.7, 1H), 7.38 (dd, *J* = 8.8, 2.5, 1H), 6.86 (d, *J* = 8.8, 1H), 4.30 (q, *J*=7.1, 2H), 3.77 (s, 3H), 1.27 (t, *J* = 7.1, 3H); ^{19}F NMR (471 MHz, $CDCl_3$) δ ppm -103.10; ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 163.5 (t, *J* = 33.6), 155.4 (t, *J* = 4.9), 132.1 (t, *J* = 1.7), 126.5 (t, *J* = 7.9), 125.8, 123.4 (t, *J* = 24.4), 112.8, 111.5 (t, *J* = 247.8), 62.9, 56.1, 13.9; IR (KBr, cm^{-1}): ν_{max} = 2983, 2945, 1773, 1495, 1270, 1110, 1021, 816, 684. HRMS m/z(ESI) calcd. for $C_{11}H_{12}ClF_2O_3$ (M + H) 265.0438, found 265.0443.

Ethyl 2,2-difluoro-2-(5-fluoro-2-methoxyphenyl)acetate (3l)

Colorless liquid (59.6 mg, 48%).^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.34 (dd, *J* = 8.5, 3.1, 1H), 7.13 (td, *J* = 8.8, 3.0, 1H), 6.88 (dd, *J* = 8.0, 4.0, 1H), 4.31 (q, *J* = 7.1, 2H), 3.77 (s, 3H), 1.28 (t, *J* = 7.1, 3H), ^{19}F NMR (471 MHz, $CDCl_3$) δ ppm -102.91(s), -122.39 (m); -102.10(d, *J* = 7.8); ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 163.6(t, *J* = 33.7), 156.7 (d, *J* = 240.2), 152.3 - 152.9(m), 123.3 (td, *J* = 24.6, 7.6), 118.6(d, *J* = 22.9), 113.8 (dt, *J* = 26.0, 7.8), 112.8 (d, *J* = 7.9), 111.5 (t, *J* = 249.1), 62.9, 56.3, 13.9; IR (KBr, cm^{-1}): ν_{max} = 2982, 1772, 1502, 1273, 1088, 1027, 887, 720.

Methyl 3-(2-ethoxy-1,1-difluoro-2-oxoethyl)-4-methoxybenzoate (3m)

Colorless liquid (77.8 mg, 54%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ ppm 8.30 (d, *J* = 2.2 Hz, 1H), 8.14 (dd, *J* = 8.7, 2.1 Hz, 1H), 6.96 (d, *J* = 8.7 Hz, 1H), 4.29 (q, *J* = 7.1 Hz, 2H), 3.88 (s, 3H), 3.85 (s, 3H), 1.26 (t, *J* = 7.1 Hz, 3H).^{19}F NMR (471 MHz, Chloroform-*d*) δ ppm -103.30 .^{13}C NMR (126 MHz, Chloroform-*d*) δ ppm 166.0, 163.6 (t, *J* = 33.8 Hz), 160.2 (t, *J* = 4.6 Hz), 134.4 (t, *J* = 1.4 Hz), 128.3 (t, *J* = 7.6 Hz), 122.8, 122.0 (t, *J* = 24.5 Hz), 111.8 (t, *J* = 249.1 Hz), 111.0, 62.8, 56.1, 52.2, 13.9; IR (KBr, cm-1): ν_{max} = 2986, 2954, 1776, 1722, 1616, 1309, 1275, 1112, 1030, 771, 682. HRMS m/z(ESI) calcd. for $C_{13}H_{15}F_2O_5$ (M + H) 289.0882, found 289.0886.

Ethyl 2,2-difluoro-2-(naphthalen-1-yl)acetate（3n）

Colorless liquid (111.3 mg, 89%). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 8.32 (d, *J* = 8.7, 1H), 7.97 (d, *J* = 8.3, 1H), 7.94 (d, *J* = 7.2, 1H), 7.91 (d, *J* = 8.2, 1H), 7.64-7.58 (m, 1H), 7.58-7.51 (m, 2H), 4.31 (q, *J* = 7.2, 2H), 1.24 (t, *J* = 7.2, 3H); ^{19}F NMR (471 MHz, $CDCl_3$) δ ppm -99.85; ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 164.46 (t, *J* = 34.8), 133.93, 132.02, 129.40, 128.94, 128.50 (t, *J* = 23.2), 127.39, 126.36, 124.94 (t, *J* = 9.4), 124.60, 124.23 (t, *J* = 3.1), 114.50 (t, 253.2), 63.30, 13.78; IR (KBr, cm^{-1}): ν_{max} = 3057, 2986, 1765, 1285, 1127, 1089, 1019, 804, 779.

Ethyl 2-(anthracen-9-yl)-2,2-difluoroacetate (3o)

Colorless liquid (130.5 mg, 87%). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 8.65 (d, *J* = 9.1, 2H), 8.57 (s, 1H), 8.01 (d, *J* = 7.8, 2H), 7.58 (t, *J* = 6.5, 2H), 7.49 (t, *J* = 7.1, 2H), 4.34 (q, *J* = 7.1, 2H), 1.26 (t, *J* = 7.2, 3H); ^{19}F NMR (471 MHz, $CDCl_3$) δ ppm *major*: -89.26; *minor*: -97.95; *minor*: -100.49; ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 164.78 (t, *J* = 34.8), 132.66, 131.47, 130.24, 129.25, 127.34, 125.42 (t, *J* = 8.9), 125.17, 123.56 (t, *J* = 23.6), 117.10 (t, *J* = 254.1), 63.57, 14.00. HRMS m/z(ESI) calcd. for $C_{13}H_{15}F_2O_5$ (M + H) 289.0882, found 289.0886.

Ethyl 2,2-difluoro-2-(thiophen-2-yl)acetate (3p)

Colorless liquid (85.6 mg, 83%). ^{1}H NMR (500 MHz, CDCl3) δ ppm 7.48 (d, J = 4.9, 1H), 7.39 (d, J = 3.6, 1H), 7.06 (t, J = 3.8, 1H), 4.36 (q, J = 7.1, 2H), 1.34 (t, J = 7.1, 3H); ^{19}F NMR (471 MHz, $CDCl_3$) δ-92.78; ^{13}C NMR (126 MHz, CDCl3) δ ppm 163.40 (t, J = 35.1), 134.11 (t, J = 30.2), 129.12, 128.58 (t, J = 5.5), 127.24, 111.85 (t, J = 250.3), 63.55, 13.93; IR (KBr, cm^{-1}): ν_{max} = 3096, 2963, 1729, 1655, 1406, 1239, 1057, 738, 672.

2-(2,5-dimethylphenyl)-2,2-difluoro-1-morpholinoethanone (3q)

Colorless liquid (70.0 mg, 52%). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.27 (s, 1H), 7.18 - 7.10 (m, 2H), 3.71 (s, 4H), 3.50 (s, 4H), 2.34 (s, 3H), 2.32 (s, 3H), ^{19}F NMR (470 MHz, $CDCl_3$) δ ppm -94.04, ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 162.2 (t, J = 30.7 Hz), 135.4, 133.5 (t, J = 2.9 Hz), 132.1, 131.6 (t, J = 22.8 Hz), 131.4, 126.1 (t, J = 8.1 Hz), 116.5 (t, J = 251.2 Hz), 66.7, 66.4, 46.7 (t, J = 4.1 Hz), 43.5, 20.9, 19.4 (t, J = 2.2 Hz); IR (KBr, cm^{-1}): ν_{max} = 2967, 2924, 2858, 1676, 1444, 1257, 1112, 1073, 820, 757. HRMS m/z(ESI) calcd. for $C_{14}H_{18}F_2NO_2$ (M + H) 270.1300, found 270.1304.

Diethyl ((2,5-dimethylphenyl)difluoromethyl)phosphonate (3r)

Colorless liquid (58.5 mg, 40%). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.24 (s, 1H), 7.07-7.01 (m, 2H), 4.10 (m, 2H), 4.02 (m, 2H), 2.42 (s, 3H), 2.26 (s, 3H), 1.26 (t, J = 7.1 Hz, 6H), ^{19}F NMR (470 MHz, $CDCl_3$) δ ppm -104.21 (dd, J = 117.3, 3.5 Hz), ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 135.2, 134.4 (q, J = 2.8 Hz), 132.2 (d, J = 1.4 Hz), 131.4 (q, J = 1.8 Hz), 130.3 (td, J = 20.2, 13.5 Hz), 128.1 (td, J = 9.1, 2.3 Hz), 119.8 (td, J = 264.4, 217.7 Hz), 64.7, 64.6, 20.9, 20.2 (t, J = 4.2 Hz), 16.4,16.3. HRMS m/z(ESI) calcd. for $C_{13}H_{20}F_2O_3P$ (M + H) 293.1113, found 293.1115.

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Keywords: Difluoromethylation • Radical • Silver-mediated • Regioselectivity • Arenes

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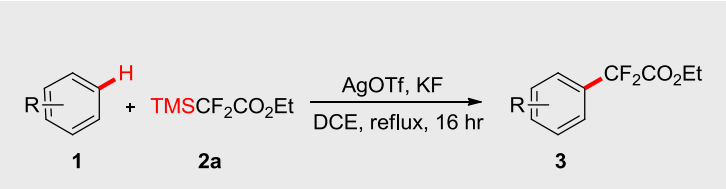

The first Ag(I)-mediated C-H difluoromethylation of arenes has been developed through an electrophilic radical-type pathway.

- Radical Difluoromethylation

Difluoromethylation*

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Silver-mediated C-H Difluoromethylation of Arenes