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Direct ethoxycarbonyldifluoromethylation of aromatic compounds using Fenton reagent

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ABSTRACT

Direct ethoxycarbonyldifluoromethylation of aromatic compounds by $BrCF_2CO_2Et$ was investigated using Fenton reagent in dimethylsulfoxide. Various five-membered hetero-aromatic compounds, benzene derivatives and uracil having ethoxycarbonyldifluoromethyl group were obtained catalytically with the combination of ferrocene and H_2O_2 at room temperature. The ethoxycarbonyldifluoromethylation occurred at the position predicted by the trend of the electrophilic substitution of aromatic compounds. When *para*-substituted aniline derivatives were used as a substrate, the one-pot synthesis of 3,3-difluoro-2,3-dihydroindole-2-one derivatives was achieved through the ethoxycarbonyldifluoromethylation at the *ortho*-position to the amino group and the consecutive intramolecular amidation of the amino group and the adjacent ethoxycarbonyldifluoromethyl group.

1. Introduction

Organic compounds possessing fluorine atoms have attracted much attention in the fields of medicines, agricultural chemicals, and functional materials.[1] Aromatic compounds having alkoxycarbonyldifluoromethyl group are important compounds because they frequently show biologically activity.[2] In addition, they can be used as synthetic intermediates by utilizing the chemical convertibility of the difluoromethylene and alkoxycarbonyl parts to the other functional groups.[3] These compounds are generally and conveniently synthesized from oxoarylacetate esters by difluorination of the α-carbonyl carbon of the alkoxal group with (diethylamino)sulfur trifluoride (DAST).[4] However, this difluorination process is unsuitable for practical use due to the toxic and explosive nature of DAST. Moreover, the ability of DAST to fluorinate hydroxyalkyl, acyl, and carboxyl groups restricts usable substrates.[5]

Direct alkoxycarbonyldifluoromethylation is considered to be an industrially promising reaction, and it has been explored by some researchers. In all previously reported reactions, difluorohaloacetate esters (XCF_2CO_2R, X=Br or Cl, and R=alkyl) or their derivatives were used as a starting material. The coupling of an aryl iodide and $BrCF_2CO_2Et$ proceeds smoothly in the presence of a Cu reagent. Although this coupling is very simple, it requires a Cu reagent more than 1.0 equiv to a substrate.[6] Direct ethoxycarbonyldifluoromethylation of aromatic compounds by an ethoxycarbonyldifluoromethyl radical was also reported. The reaction of $BrCF_2CO_2Et$ and PhSe–SePh provides $PhSe–CF_2CO_2Et$ from which an ethoxycarbonyldifluoromethyl radical is generated under photoirradiation.[7] The drawback of this reaction is the high toxicity of selenium. An ethoxycarbonyldifluoromethyl radical is also generated from $ClCF_2CO_2Et$ in the presence of $Na_2S_2O_4$ and $NaHCO_3$. This reaction has the advantage of proceeding with $ClCF_2CO_2Et$, which is less expensive than $BrCF_2CO_2Et$.[8]

Recently, we found that the radical trifluoromethylation of various nucleobases, benzene derivatives and five- and six-membered hetero-aromatic compounds by CF_3I was successfully achieved using the Fenton reagent comprising of $FeSO_4$ or ferrocene (Cp_2Fe) and H_2O_2 as a catalyst in dimethylsulfoxide (DMSO).[9] This trifluoromethylation can be used in an industrial process, because it is a simple reaction with the inexpensive materials. Indeed, 5-trifluoromethyluracil (5-TFU) is currently manufactured by this trifluoromethylation of uracil in a one-step process.

We began our investigation at the point that the Fenton reagent should generate an ethoxycarbonyldifluoromethyl radical from $BrCF_2CO_2Et$. Herein, we report that the Fenton reagent in DMSO efficiently catalyzed the direct ethoxycarbonyldifluoromethylation of various aromatic compounds by $BrCF_2CO_2Et$. Furthermore, this report describes the one-pot synthesis of 3,3-difluoro-2,3-dihydroindole-2-one derivatives from *para*-substituted aniline derivatives through ethoxycarbonyldifluoromethylation and consecutive intramolecular amidation.

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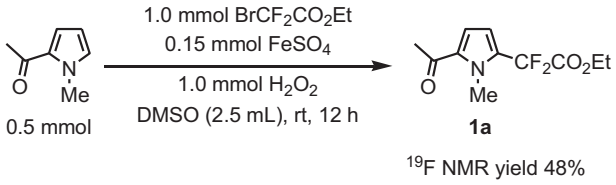
2. Results and discussion

2.1. Ethoxycarbonyldifluoromethylation of aromatic compounds

First, we examined the ethoxycarbonyldifluoromethylation of 2-acetyl-1-methylpyrrole using $FeSO_4 \cdot 7H_2O$; $FeSO_4$ is generally used in the Fenton reaction because of its cost and availability.[10] When a 30% aqueous solution of H_2O_2 was added dropwise to the solution of 2-acetyl-1-methylpyrrole, $FeSO_4 \cdot 7H_2O$, and $BrCF_2CO_2Et$ in DMSO, followed by stirring at room temperature for 12 h, only ethyl (5-acetyl-1-methylpyrrol-2-yl)difluoroacetate (**1a**) was detected by ^{19}F NMR with 48% yield (Scheme 1).



Scheme 1.

The selective formation of **1a** suggests that the reaction in Scheme 1 is one of the electrophilic substitution, which generally occurs on the adjacent carbon of the nitrogen in *N*-substituted pyrroles.[11] An ethoxycarbonyldifluoromethyl radical should possess an electrophilic character owing to the electron-withdrawing nature of fluorine and ethoxycarbonyl group. Taking into account this character of an ethoxycarbonyldifluoromethyl radical, it is reasonable to assume that an orientation similar to the electrophilic substitution of aromatic compounds was observed in Scheme 1. The trifluoromethylation in which an electrophilic trifluoromethyl radical participates occurred along with the same orientation as in Scheme 1; 2-acetyl-1-methyl-5-trifluoromethylpyrrole was selectively obtained from the same substrate.[9b]

In the trifluoromethylation of 2-acetyl-1-methylpyrrole, Cp_2Fe provided a higher yield than $FeSO_4$.[9b] When we examined the ethoxycarbonyldifluoromethylation of 2-acetyl-1-methylpyrrole with various Fe(II) compounds, Cp_2Fe gave a higher yield than the other inorganic and organic Fe(II) compounds as shown in Table 1. Although the reason for the availability of Cp_2Fe in the reaction with 2-acetyl-1-methylpyrrole cannot be explained at present, we believe that the present reaction is one of the rare examples of the Fenton reaction with Cp_2Fe or its derivatives as well as the trifluoromethylation reported previously.[9,12]

Next we optimized the reaction conditions. In the trifluoromethylation by CF_3I using the Fenton reagent, the addition of an acid was frequently profitable for the reaction.[9] In the present reaction, the addition of an acid retarded the reaction as shown in Table 2.

Table 1
Ethoxycarbonyldifluoromethylation of 2-acetyl-1-methylpyrrole with various Fe(II) compounds[a]

Entry	Fe(II)compound	^{19}F NMR yield/%
1	$FeSO_4 \cdot 7H_2O$	48
2	Cp_2Fe	60
3	$FeBr_2$	27
4	$Fe(BF_4)_2$	7
5	$Fe(NH_4)_2(SO_4)_2 \cdot 6H_2O$	6
6	$Fe(OAc)_2$	0
7	$Fe(acac)_2$	25
8	$FeCl_2 \cdot 4H_2O$	45

[a] The used amounts of Fe(II) compound, 2-acetyl-1-methylpyrrole, $BrCF_2CO_2Et$, and H_2O_2 were 0.15 mmol, 0.50 mmol, 1.0 mmol, and 1.0 mmol, respectively. All the reactions were carried out in 2.5 mL of DMSO for 12 h at room temperature.

Table 2
The effect of an acid on ethoxycarbonyldifluoromethylation of 2-acetyl-1-methylpyrrole[a]

Entry	Acid	^{19}F NMR yield/%
1	None	60
2	H_2SO_4	20
3	HCl	11
4	HBF_4	29
5	CH_3CO_2H	53
6	CF_3CO_2H	30

[a] The used amount of an acid is 1.0 mmol. The other reaction conditions were the same as those in Table 1.

Further survey of the amount of Cp_2Fe, H_2O_2 and $BrCF_2CO_2Et$ used resulted in the 88% yield of **1a**. Since the turnover number of Cp_2Fe is 8.8, it is confirmed that Cp_2Fe acts as a catalyst. On the other hand, **1a** was not obtained at all from 2-acetyl-1-methylpyrrole using $ClCF_2CO_2Et$ under the same condition. Chen and coworkers reported that several benzene derivatives were ethoxycarbonyldifluoromethylated by $ClCF_2CO_2Et$ in the presence of $Na_2S_2O_4$ and $NaHCO_3$ despite the low yields.[8] It is the disadvantage of the present ethoxycarbonyldifluoromethylation that less expensive $ClCF_2CO_2Et$ cannot be used for the reaction instead of $BrCF_2CO_2Et$.

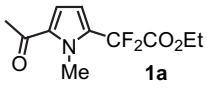
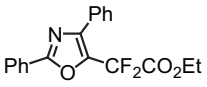
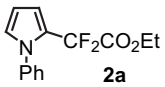
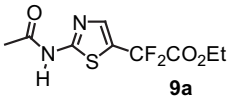
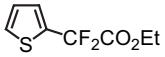
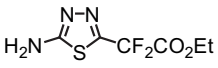
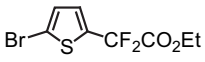
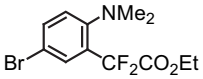
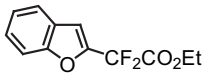
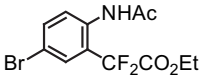
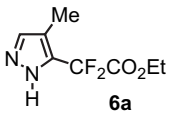
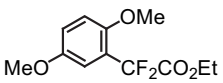
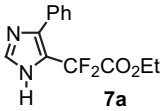
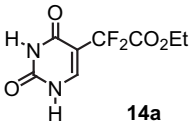
The results of the ethoxycarbonyldifluoromethylation of various aromatic compounds examined under the same conditions were listed in Table 3.

We examined the reactions in Table 3 using $FeSO_4$ and Cp_2Fe, respectively. Interestingly, Cp_2Fe gave a higher yield than $FeSO_4$ with all the substrates. This is contrast to the results of trifluoromethylation of aromatic compounds with the Fenton reagent. Thus, certain substrates preferred $FeSO_4$ to Cp_2Fe in the trifluoromethylation.[9]

Generally, five-membered hetero-aromatic compounds are highly reactive in the electrophilic substitution owing to the high π-electron density. 5-Acetyl-1-methylpyrrole (entry 1) and 1-phenylpyrrole (entry 2) provided satisfactory yields; these two compounds are particularly reactive in the electrophilic substitution. Moderate yields were obtained with the other substrates except entries 6 and 7. 4-Methylpyrazole (entry 6) and 4-phenylimidazole (entry 7) afforded rather low yields, suggesting that the 5-position of these compounds is sterically hindered by the adjacent methyl and phenyl group, respectively.[13] In contrast, 2,4-diphenyloxazole gave a moderate yield despite the presence of the phenyl group at the 4-position (entry 8). In the trifluoromethylation using the Fenton reagent, the yield of 2,4-diphenyl-5-trifluoromethyloxazole from 2,4-diphenyloxazole was also much higher than that of 4-methyl-5-trifluoromethylpyrazole from 4-methylpyrazole (80% vs 49%).[9b] We now consider that certain interactions between Fe(II) and the substrate may be favourable for the reaction though no experimental evidence supports this claim. With regard to entries 1–7 and 9, the ethoxycarbonyldifluoromethyl group was selectively introduced to the 2- or 5-position. Thus, the orientation is certainly explained based on the trend of the electrophilic substitution of aromatic compounds.[11]

It is noteworthy that the phenyl parts in **2a**, **7a**, and **8a** were not ethoxycarbonyldifluoromethylated at all.[14] This is also consistent with the trend of the electrophilic substitution because the electron density of phenyl rings is generally lower than five-membered hetero-aromatic rings. Similarly, some benzene and pyridine derivatives afforded very small yields; the latter substrates are π-electron deficient as well as benzene derivatives. On the other hand, the benzene derivatives with an electron-donating group,

Table 3
Ethoxycarbonyldifluoromethylation of various aromatic and *pseudo*-aromatic compounds[a]

Entry	Product	Isolated yield/%	Entry	Product	Isolated yield/%
1	 **1a**	88	8	 **8a**	55
2	 **2a**	83	9	 **9a**	61
3	 **3a**	60	10	 **10a**	34
4	 **4a**	63	11	 **11a**	71
5	 **5a**	45	12	 **12a**	35
6	 **6a**	27	13	 **13a**	61
7	 **7a**	14	14	 **14a**	58

[a] The used amounts of Cp_2Fe, a substrate, $BrCF_2CO_2Et$, and H_2O_2 were 0.05 mmol, 0.50 mmol, 1.5 mmol, and 1.0 mmol, respectively. All the reactions were carried out in 2.5 mL of DMSO for 12 h at room temperature.

such as dimethylamino (entry 11), acetoamide (entry 12), and methoxy (entry 13) group provided moderate yields. Based on the orientation of the electrophilic substitution, it is reasonable to assume that the products of **11a** and **12a** in entries 11 and 12 are *ortho*-orientated to the electron-donating groups. The ethoxycarbonyldifluoromethylation of uracil, a *pseudo*-aromatic compound, also occurred selectively at more electronegative 5-position than 6-position (entry 14) in the same manner as 5-TFU synthesis by the trifluoromethylation of uracil.[9a]

With regard to the present catalytic ethoxycarbonyldifluoromethylation, a reaction mechanism similar to the trifluoromethylation can be proposed.[9a] Fig. 1 depicts the speculated mechanism of the reaction using 2-acetyl-1-methylpyrrole as a substrate. Thus, (i) Fe(II) reduces H_2O_2 to a hydroxyl radical, (ii) the hydroxyl radical is rapidly trapped by the DMSO solvent to form a radical adduct **A**, (iii) a methyl radical is generated from **A**, (iv) the reaction of $BrCF_2CO_2Et$ and the methyl radical releases a CF_2CO_2Et radical, (v) the CF_2CO_2Et radical adds to the 2-position of 2-acetyl-1-methylpyrrole to form a radical species **B** and (vi) Fe(III) oxidizes **B** to **1a** and is reduced to Fe(II).

In step (i), known as the Fenton reaction, the role of a Fe(II) compound is to generate a hydroxyl radical from H_2O_2.[10] The difference in the activity of Cp_2Fe and $FeSO_4$ would practically depend on the difference in the ability of hydroxyl radical formation. If so, either Cp_2Fe or $FeSO_4$ should be favourable independent of the substrate. Nevertheless, the choice of Cp_2Fe or $FeSO_4$ depended non-regularly on the substrate in the trifluoromethylation of various nucleobases and aromatic compounds.[9] In contrast, Cp_2Fe gave a higher yield than $FeSO_4$ in the ethoxydifluoromethylcarbonylation. Therefore, the role of Cp_2Fe seems somewhat complex. Specific interaction between Cp_2Fe and $BrCF_2CO_2Et$ may accelerate the hydroxyl radical formation. The detailed investigation is now in progress.

2.2. One-pot synthesis of 3,3-difluoro-2,3-dihydroindole-2-one derivatives

Table 4 shows the results of the ethoxycarbonyldifluoromethylation of the *para*-substituted aniline derivatives. As predicted from the orientation of the electrophilic substitution, the *ortho*-position to the amino group was ethoxycarbonyldifluoromethylated. In entries 3–5, it is considered possible that a compound ethoxycarbonyldifluoromethylated at two *ortho*-positions is concomitantly formed. Actually, little such product was detected. The electron-withdrawing ethoxycarbonyldifluoromethyl group presumably decreases the π-electron density, resulting in the suppression of the second attack of the ethoxycarbonyldifluoromethyl radical on another *ortho*-position.

The reactions in Table 4 were carried out for 3 h. In the reactions for a longer time, another product was detected by ^{19}F NMR. For

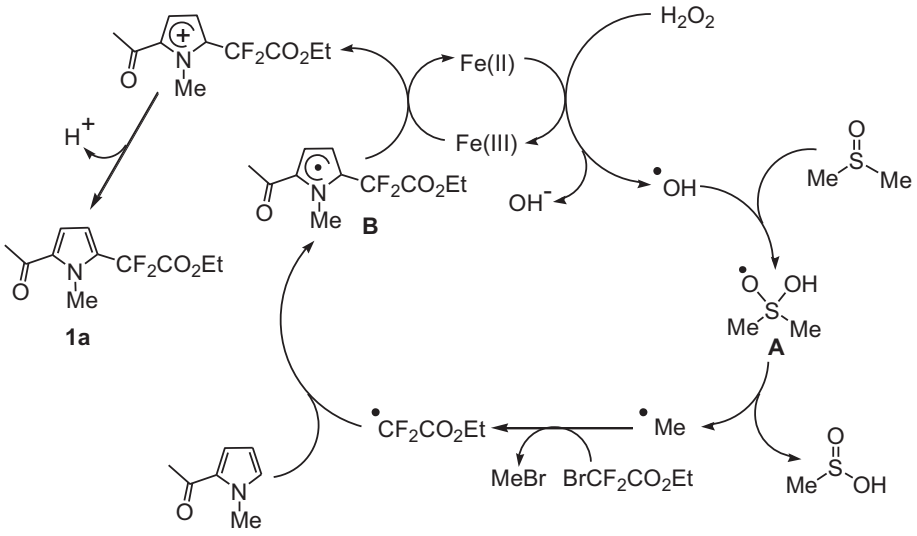
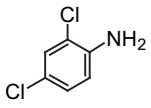
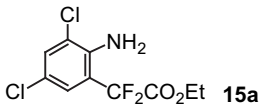
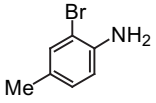
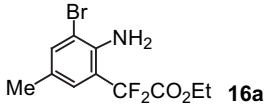
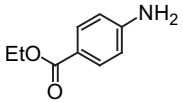
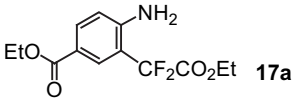
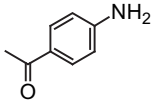
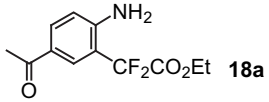
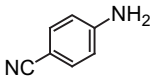
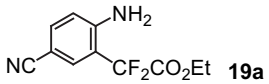


Fig. 1. Speculated mechanism of ethoxycarbonyldifluoromethylation.

Table 4
Ethoxycarbonyldifluoromethylation of various *para*-substituted aniline derivatives[a]

Entry	Substrate	Product	Isolated yield/%
1		 **15a**	44
2		 **16a**	40
3		 **17a**	38
4		 **18a**	31
5		 **19a**	27

[a] The used amounts of Cp_2Fe, a substrate, $BrCF_2CO_2Et$, and H_2O_2 were 0.1 mmol, 1.0 mmol, 3.0 mmol, and 0.2 mmol, respectively. All the reactions were carried out in 5.0 mL of DMSO for 3 h at room temperature.

example, a new peak at −110.6 ppm was found in the ^{19}F NMR spectrum after the reaction using 2,4-dichloroaniline for 6 h; the peak of **15a** appeared at −103.1 ppm. This product was isolated and characterized as 5,7-dichloro-3,3-difluoro-2,3-dihydroindol-2-one (**15b**).

The time course of the formation of **15a** and **15b** traced by ^{19}F NMR is illustrated in Fig. 2. The yield of **15a** gradually increased from the start of the reaction and reached 60% at 6 h. At this time, **15b** was detected for the first time. After that, the yield of **15a** and **15b** monotonously decreased and increased, respectively. At 60 h from the start of the reaction, only **15b** was observed with 72% yield. The behavior of both products clearly indicates the consecutive formation of **15b** from **15a**.

It is known that the intramolecular amidation of (2-aminophenyl)acetate esters to 2,3-dihydroindole-2-one derivatives occurs through the nucleophilic attack of the lone pair on the nitrogen of the amino group on the carbonyl carbon in the alkoxycarbonylmethyl group.[15,16] Considering this reaction, **15b** should be formed from **15a** through the intramolecular amidation of the amino group and the ethoxycarbonyldifluoromethyl group as shown in Scheme 2.

The intramolecular amidation of (2-aminophenyl)acetate esters to 2,3-dihydroindole-2-one derivatives is performed in the presence of an acid[15] or a base[16] under somewhat severe conditions, for example, the reaction in Ref. 15 was carried out in 1.0 M HCl at refluxing temperature. In contrast, the present reaction proceeds under mild conditions. Moreover, H_2O_2, which is considered to act as an acid for the intramolecular amidation, is not so strong acid and is consumed during the reaction. In the reaction in Scheme 2, the electron-withdrawing fluorine atoms in the ethoxycarbonyldifluoromethyl

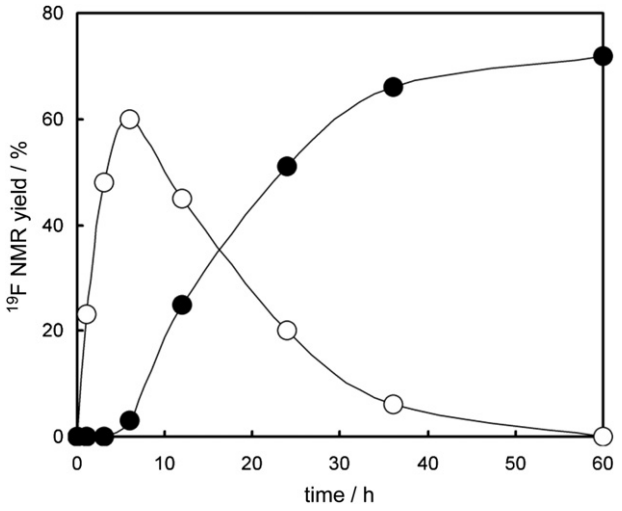
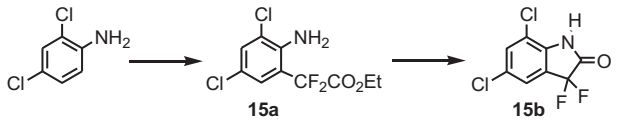


Fig. 2. Time-course of the yield of **15a** (○) and **15b** (●). The reaction conditions except the reaction time are the same as those in Table 4.



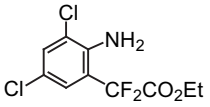
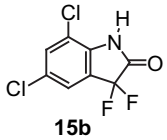
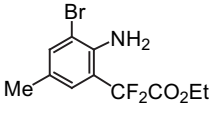
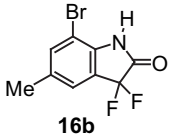
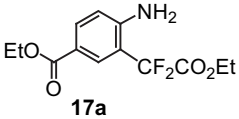
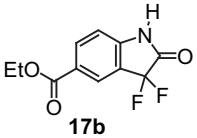
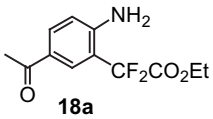
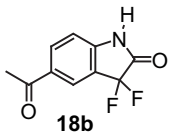
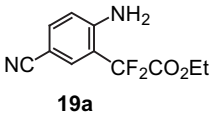
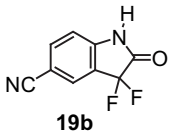
Scheme 2.

group probably enhance the electrophilicity of the carbonyl carbon, resulting in the acceleration of the nucleophilic attack of the nitrogen in the amino group.

Table 5 lists the yields of the intramolecular amidation of isolated **15a**–**19a** in the presence of various acids or bases. The desired products were obtained with satisfactory yields in all entries even at room temperature.

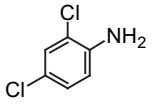
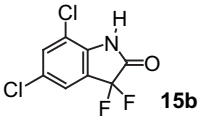
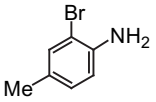
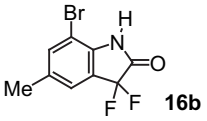
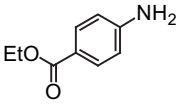
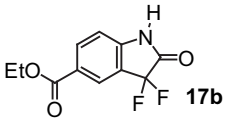
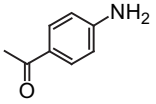
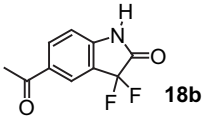
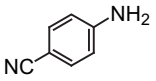
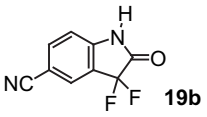
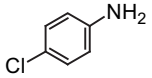
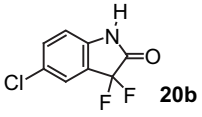
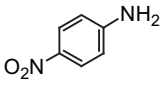
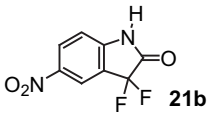
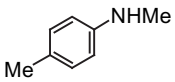
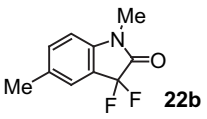
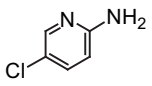
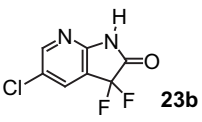
The results in Table 5 suggest that the extra addition of an acid can accelerate the formation of **15b** from 2,4-dichloroaniline via **15a** in the reaction shown in Fig. 2; a base that should neutralize H_2O_2 is unfit for the extra addition. However, Table 2 reveals that the addition of an acid is unsuitable for the first ethoxycarbonyldifluoromethylation step in Scheme 2. Indeed, when the reaction was carried out in the presence of 1.0 mmol of H_2SO_4 at the start of the reaction, the yield of **15b** was only 17% even after 24 h. Then we focused on the behavior of the formation of **15a** and **15b** in Fig. 2. The sum of the yields of **15a** and **15b** was ca. 70% at 12 h and it remained at this value thereafter. This behavior implies the ethoxycarbonyldifluoromethylation in Scheme 2 was completed after around 12 h. Therefore, the addition of an acid at 12 h from the start of the reaction should not retard the first step and should accelerate the second intramolecular amidation step. Then, we added H_2SO_4 at 12 h from the start of the reaction and continued the reaction for another 12 h. As a result, only **15b** was successfully obtained with 73% yield, which is virtually the same as the yield (72%) obtained at 60 h in Fig. 2. This result prompted us to examine the one-pot synthesis of 3,3-difluoro-2,3-dihydroindole-2-one derivatives from *para*-substituted aniline derivatives through the ethoxycarbonyldifluoromethylation and the addition of H_2SO_4 in the middle of the reaction. Table 6 shows the results of the

Table 5
Intramolecular amidation of the ethoxycarbonyldifluoromethylated *para*-substituted aniline derivatives to 2,3-dihydroindole-2-one derivatives[a]

Entry	Substrate	Product	Acid or base	Isolated yield/%
1	 **15a**	 **15b**	H_2SO_4	99
			NEt_3	98
			K_2CO_3	98
2	 **16a**	 **16b**	HCl	70
			NEt_3	81
3	 **17a**	 **17b**	H_2SO_4	95
4	 **18a**	 **18b**	CF_3CO_2H	98
5	 **19a**	 **19b**	CF_3CO_2H	91

[a] The used amounts of a solvent (DMSO, CH_2Cl_2 or DMF) and a substrate were 1.0–3.0 mL and 0.2–0.75 mmol, respectively. The ratios of [acid or base]/[substrate] were 2.0–14.4. The reactions were carried out for 6–24 h at room temperature.

Table 6
One-pot synthesis of 3,3-difluoro-2,3-dihydroindole-2-one derivatives[a]

Entry	Substrate	Product	Isolated yield/%
1		 **15b**	72
2		 **16b**	75
3		 **17b**	58
4		 **18b**	43
5		 **19b**	45
6		 **20b**	50
7		 **21b**	13
8		 **22b**	38
9		 **23b**	21

[a] The used amounts of Cp_2Fe, a substrate, $BrCF_2CO_2Et$, and H_2O_2 were 0.1 mmol, 1.0 mmol, 3.0 mmol, and 0.2 mmol, respectively. All the reactions were carried out in 5.0 mL of DMSO for 24 h at room temperature.

reactions using various *para*-substituted aniline derivatives as a substrate. We obtained the products **15b**–**23b** despite the somewhat low yield. The substrates having a protected amino group (entry 8) or pyridine ring (entry 9) also provided 3,3-difluoro-2,3-dihydroindole-2-one derivatives despite the low yield, suggesting that the present one-pot reaction can be applied to a wide variety of substrates.

3,3-Difluoro-2,3-dihydroindole-2-one derivatives are known to be biologically active[17] and are generally synthesized from 1*H*-indole-2,3-dione derivatives by fluorination with DAST.[4,18] Since the syntheses of 1*H*-indole-2,3-dione derivatives require the several steps from aniline derivatives,[19] our synthetic method is superior to this method not only because of the safety and versatility considerations, as described in Introduction, but also because of its relative simplicity.

3. Conclusion

Here we presented the direct ethoxycarbonyldifluoromethylation of various aromatic compounds by $BrCF_2CO_2Et$ using the Fenton reagent as a catalyst in DMSO. Of the Fe(II) compounds tested, Cp_2Fe showed the highest catalytic activity. The selectivity of a product was predicted by the general trend of the electrophilic substitution of aromatic compounds, indicating that an electrophilic ethoxycarbonyldifluoromethyl radical participates in the reaction. Moreover, 3,3-difluoro-2,3-dihydroindole-2-one derivatives were successfully synthesized from the corresponding *para*-substituted aniline derivatives in the one-pot reaction. The present catalytic reaction is a simple procedure, that is, carried out under mild conditions with inexpensive materials; therefore, it should serve as a promising process for the synthesis of fluorinated organic compounds.

4. Experimental

4.1. General techniques

^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded in $CDCl_3$, DMSO-d_6 or CD_3CO_2D using Bruker DRX-500 (^{1}H 500 MHz, ^{13}C 125 MHz) and DRX-250 (^{19}F 235 MHz) spectrometers using tetramethylsilane as an internal reference for ^{1}H and ^{13}C NMR and fluorotrichloromethane as an external reference for ^{19}F NMR. Chemical shifts were expressed in parts per million (δ). Multiplicties were indicated by s (singlet), br s (broad singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). ^{19}F NMR yields were calculated with 2,2,2-trifluoroethanol as an internal standard. The IR, high-resolution mass spectroscopy (HRMS), and melting point (mp) measurements were carried out using HORIBA FT-720, Waters LCT Premier XE, and Stanford Research Systems MPA100, respectively. IR spectra were obtained in the reflective mode. All the commercially available reagents were used without further purification.

4.2. General procedure

4.2.1. Ethoxycarbonyldifluoromethylation of aromatic compounds. A substrate (0.5 mmol), Cp_2Fe (9.3 mg, 0.05 mmol), $BrCF_2CO_2Et$ (194 μL, 1.5 mmol), and DMSO (2.5 mL) were charged in a two-neck flask in Ar atmosphere. Then, a 30% aqueous solution of H_2O_2 (0.10 mL, H_2O_2 1.0 mmol) was added continuously over 2.5 min. The reaction mixture was stirred at room temperature for 12 h. The reaction mixture was poured into H_2O and the product was extracted to ethyl acetate. The ethyl acetate layer was washed with a saturated aqueous solution of NaCl, dried with Na_2SO_4, and then concentrated under vacuo. The product was isolated using silica gel chromatography.

4.2.2. Intramolecular amidation of ethyl (2-aminophenyl)difluoroacetate. The synthetic procedure of 5,7-dicholoro-3,3-difluoro-2,3-dihydroindole-2-one is used as an example hereinafter. Ethyl (2-amino-3,5-dicholorophenyl)difluoroacetate (0.75 mmol) and DMSO solution of H_2SO_4 (1.0 M, 1.5 mL) were charged in a two-neck flask in Ar atmosphere. The mixture was stirred at room temperature for 12 h. The reaction mixture was poured into H_2O and the product was extracted to ethyl acetate. The ethyl acetate layer was washed with a saturated aqueous solution of NaCl, dried with Na_2SO_4, and then concentrated under vacuo. The product was isolated using silica gel chromatography.

4.2.3. One-pot synthesis of 3,3-difluoro-2,3-dihydroindole-2-one derivatives. A substrate (1.0 mmol), Cp_2Fe (19 mg, 0.1 mmol), $BrCF_2CO_2Et$ (388 μL, 3.0 mmol), and DMSO (5.0 mL) were charged in a two-neck flask in Ar atmosphere. Then, a 30% aqueous solution of H_2O_2 (0.20 mL, H_2O_2 2.0 mmol) was added continuously over 5 min. The reaction solution was stirred at room temperature for 12 h. After adding 2.0 mL of DMSO solution of H_2SO_4 (1.0 M) to the reaction mixture, the mixture was stirred for another 24 h at room temperature. The reaction mixture was poured into H_2O and the product was extracted to ethyl acetate. The ethyl acetate layer was washed with a saturated aqueous solution of NaCl, dried with Na_2SO_4, and then concentrated under vacuo. The product was isolated using silica gel chromatography.

4.3. Characterization of products

*4.3.1. Ethyl (5-acetyl-1-methylpyrrole-2-yl)difluoroacetate (**1a**).* Colorless oil. ^{1}H NMR (DMSO-d_6) δ 1.26 (3H, t, J=7.1 Hz), 2.43 (3H, s), 3.89 (3H, s), 4.39 (2H, q, J=7.1 Hz), 6.51 (1H, d, J=4.3 Hz), 7.12 (1H, d, J=4.3 Hz). ^{13}C NMR (DMSO-d_6) δ 13.8, 28.0, 34.4, 64.2, 110.7 (t, J_{CF}=247.4 Hz), 111.0 (t, J_{CF}=5.5 Hz), 118.4, 129.3 (t, J_{CF}=28.8 Hz), 133.9, 162.1 (t, J_{CF}=33.5 Hz), 189.8. ^{19}F NMR (DMSO-d_6) δ −97.7. IR 1765, 1666, 1383, 1300, 1240, 1184, 1101, 1016, 904, 779, 746 cm^{-1}. HRMS: calcd for $C_{11}H_{13}F_2NO_3$ (M+H$^+$): 246.0936; found: m/z 246.0945.

*4.3.2. Ethyl (1-phenylpyrrole-2-yl)difluoroacetate (**2a**).* Pale yellow oil. ^{1}H NMR ($CDCl_3$) δ 1.21 (3H, t, J=7.1 Hz), 4.14 (2H, q, J=7.1 Hz), 6.26–6.29 (1H, m), 6.61–6.64 (1H, m), 6.85–6.88 (1H, m), 7.34–7.45 (5H, m). ^{13}C NMR ($CDCl_3$) δ 13.7, 63.0, 108.4, 110.7 (t, J_{CF}=246.0 Hz), 112.9 (t, J_{CF}=5.2 Hz), 124.3 (t, J_{CF}=30.0 Hz), 126.9, 127.2, 128.3, 128.8, 139.3, 163.1 (t, J_{CF}=34.0 Hz). ^{19}F NMR (DMSO-d_6) δ −90.9. IR 1763, 1500, 1302, 1257, 1092, 1070, 1036, 939, 768, 731, 696 cm^{-1}. EI-MS: calcd for $C_{14}H_{13}F_2NO_2$ (M): 265.091; found: m/z 265. Full characterization is shown in Ref. 7b.

*4.3.3. Ethyl (thiophene-2-yl)difluoroacetate (**3a**).* Colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.36 (3H, t, J=7.1 Hz), 4.37 (2H, q, J=7.1 Hz), 7.04–7.10 (1H, m), 7.37–7.42 (1H, m), 7.46–7.51 (1H, m). ^{13}C NMR ($CDCl_3$) δ 13.8, 63.4, 110.7 (t, J_{CF}=250.4 Hz), 127.1, 128.4 (t, J_{CF}=5.6 Hz), 129.0 (t, J_{CF}=1.5 Hz), 134.0 (t, J_{CF}=30.1 Hz), 163.3 (t, J_{CF}=35.1 Hz). ^{19}F NMR (DMSO-d_6) δ −90.8. EI-MS: calcd for $C_8H_8F_2O_2S$ (M): 206.021; found: m/z 206. Full characterization is shown in Ref. 3b.

*4.3.4. Ethyl (5-bromothiophene-2-yl)difluoroacetate (**4a**).* Colorless oil. ^{1}H NMR (DMSO-d_6) δ 1.27 (3H, t, J=7.1 Hz), 4.37 (2H, q, J=7.1 Hz), 7.32–7.35 (1H, m), 7.36–7.39 (1H, m). ^{13}C NMR (DMSO-d_6) δ 13.7, 64.2, 110.9 (t, J_{CF}=249.6 Hz), 116.8, 130.5 (t, J_{CF}=5.9 Hz), 131.3, 134.0 (t, J_{CF}=30.2 Hz), 162.0 (t, J_{CF}=34.2 Hz). ^{19}F NMR (DMSO-d_6) δ −91.6. IR 1765, 1431, 1290, 1232, 1093, 1011, 978, 802, 750 cm^{-1}. EI-MS: calcd for $C_8H_7BrF_2O_2S$ (M): 283.932; found: m/z 284. HRMS and elementary analysis showed little reliability probably due to high volatility and/or low thermal and chemical stability.

*4.3.5. Ethyl (benzo[b]furane-2-yl)acetate (**5a**).* Pale yellow oil. ^{1}H NMR (DMSO-d_6) δ 1.28 (3H, t, J=7.1 Hz), 4.41 (2H, q, J=7.1 Hz), 7.35–7.40 (1H, m), 7.46–7.51 (1H, m), 7.54 (1H, s), 7.70–7.74 (1H, m), 7.76–7.80 (1H, m). ^{13}C NMR (DMSO-d_6) δ 13.8, 64.3, 109.0 (t, J_{CF}=247.5 Hz), 109.3 (t, J_{CF}=4.1 Hz), 112.1, 122.9, 124.3, 126.2, 127.2, 145.4 (t, J_{CF}=32.1 Hz), 154.9, 161.4 (t, J_{CF}=32.6 Hz). ^{19}F NMR (DMSO-d_6) δ −102.4. IR 1766, 1290, 1254, 1169, 1101, 1026, 827, 746 cm^{-1}. EI-MS: calcd for $C_{12}H_{10}F_2O_3$ (M): 240.060; found: m/z 240. HRMS and elementary analysis showed little reliability probably due to high volatility and/or low thermal and chemical stability.

*4.3.6. Ethyl difluoro(4-methylpyrazole-5-yl)acetate (**6a**).* Pale yellow oil. ^{1}H NMR (DMSO-d_6) δ 1.25 (3H, t, J=7.1 Hz), 2.10 (3H, s), 4.33 (2H, q, J=7.1 Hz), 7.67 (1H, s), 13.06 (1H, br s). ^{13}C NMR (DMSO-d_6) δ 8.1, 13.9, 63.2, 112.9 (t, J_{CF}=243.3 Hz), 114.0, 130.0, 141.9 (t, J_{CF}=26.4 Hz), 163.3 (t, J_{CF}=32.6 Hz). ^{19}F NMR (DMSO-d_6) δ −98.7. IR 3172, 2939, 1763, 1296, 1250, 1080, 1014, 835, 818, 773, 739 cm^{-1}. HRMS: calcd for $C_8H_{10}F_2N_2O_2$ (M+H$^+$): 205.0783; found: m/z 205.0791.

*4.3.7. Ethyl difluoro(4-phenylimidazole-5-yl)acetate (**7a**).* White solid. Mp 149 °C (dec). ^{1}H NMR (DMSO-d_6) δ 1.18 (3H, t, J=7.1 Hz), 4.23 (2H, q, J=7.1 Hz), 7.38–7.43 (1H, m), 7.44–7.50 (2H, m), 7.51–7.56 (2H, m), 7.81 (1H, s), 13.00 (1H, br s). ^{13}C NMR (CD_3CO_2D) δ 13.9, 64.3, 112.4 (t, J_{CF}=246.6 Hz), 127.2 (t, J_{CF}=30.5 Hz), 129.5, 129.6, 129.8, 130.1, 133.8, 137.6, 164.1 (t, J_{CF}=33.8 Hz). ^{19}F NMR (DMSO-d_6) δ −94.9. IR 1751, 1493, 1469, 1298, 1130, 1088, 1059, 953, 777, 700, 658 cm^{-1}. HRMS: calcd for $C_{13}H_{12}F_2N_2O_2$ (M+H$^+$): 267.0945; found: m/z 267.0943.

*4.3.8. Ethyl difluoro(2,4-diphenyloxazole-5-yl)acetate (**8a**).* White solid. Mp 47.3–48.8 °C. ^{1}H NMR (DMSO-d_6) δ 1.16 (3H, t, J=7.1 Hz), 4.29 (2H, q, J=7.1 Hz), 7.50–7.56 (3H, m), 7.58–7.64 (3H, m), 7.68–7.72 (2H, m), 8.03–8.07 (2H, m). ^{13}C NMR (DMSO-d_6) δ 13.6, 64.4, 109.1 (t, J_{CF}=247.9 Hz), 125.5, 126.8, 128.4, 128.8, 129.3, 129.5, 129.8, 132.1, 135.6 (t, J_{CF}=34.2 Hz), 142.3 (t, J_{CF}=2.4 Hz), 161.1 (t,

J_{CF}=34.0 Hz), 161.4. ^{19}F NMR (DMSO-d_6) δ −99.1. IR 1770, 1450, 1365, 1286, 1084, 953, 781, 715, 688 cm^{-1}. HRMS: calcd for $C_{19}H_{15}F_2NO_3$ (M+H$^+$): 344.1098; found: *m*/*z* 344.1094.

*4.3.9. Ethyl (2-acetoamidethiazole-5-yl)difluoroacetate (**9a**).* White solid. Mp 142.7–144.2 °C. ^{1}H NMR (DMSO-d_6) δ 1.27 (3H, t, J=7.1 Hz), 2.17 (3H, s), 4.37 (2H, q, J=7.1 Hz), 7.83 (1H, s), 12.54 (1H, br s). ^{13}C NMR (DMSO-d_6) δ 13.8, 22.5, 64.1, 111.8 (t, J_{CF}=248.1 Hz), 120.7 (t, J_{CF}=29.1 Hz), 139.9 (t, J_{CF}=6.6 Hz), 161.1, 162.4 (t, J_{CF}=34.4 Hz), 169.5. ^{19}F NMR (DMSO-d_6) δ −90.6. IR 2922, 1766, 1693, 1562, 1535, 1248, 1173, 1119, 1086, 999, 957, 746 cm^{-1}. HRMS: calcd for $C_9H_{10}F_2N_2O_3S$ (M+H$^+$): 265.0458; found: *m*/*z* 265.0465.

*4.3.10. Ethyl (5-amino-1,3,4-thiadiazole-2-yl)difluoroacetate (**10a**).* Yellow solid. Mp 172 °C (dec). ^{1}H NMR (DMSO-d_6) δ 1.27 (3H, t, J=7.1 Hz), 4.38 (2H, q, J=7.1 Hz), 7.91 (2H, br s). ^{13}C NMR (DMSO-d_6) δ 13.8, 64.2, 110.2 (t, J_{CF}=248.2 Hz), 148.2 (t, J_{CF}=31.0 Hz), 161.2 (t, J_{CF}=31.7 Hz), 171.6. ^{19}F NMR (DMSO-d_6) δ −94.9. IR 3271, 3087, 1635, 1398, 1267, 1119, 1093, 1066, 995, 812, 760 cm^{-1}. HRMS: calcd for $C_6H_7F_2N_3O_2S$ (M+H$^+$): 224.0305; found: *m*/*z* 224.0309.

*4.3.11. Ethyl 2-(4-bromo-2-dimethylaminophenyl)-2,2-difluoroacetate (**11a**).* Colorless oil. ^{1}H NMR (DMSO-d_6) δ 1.21 (3H, t, J=7.1 Hz), 2.47 (6H, s), 4.25 (2H, q, J=7.1 Hz), 7.49–7.53 (1H, m), 7.76–7.80 (2H, m). ^{13}C NMR (DMSO-d_6) δ 14.0, 45.0, 62.5, 111.8 (t, J_{CF}=246.7 Hz), 117.9, 126.1, 128.5 (t, J_{CF}=6.9 Hz), 132.3 (t, J_{CF}=23.9 Hz), 135.6, 151.8 (t, J_{CF}=4.9 Hz), 162.7 (t, J_{CF}=32.4 Hz). ^{19}F NMR (DMSO-d_6) δ −97.7. IR 1770, 1487, 1255, 1232, 1088, 1065, 1024, 941, 741, 675 cm^{-1}. HRMS: calcd for $C_{12}H_{14}BrF_2NO_2$ (M+H$^+$): 322.0254; found: *m*/*z* 322.0239.

*4.3.12. Ethyl 2-(2-acetylamino-4-bromophenyl)-2,2-difluoroacetate (**12a**).* Pale yellow solid. Mp 97.5–98.7 °C ^{1}H NMR (DMSO-d_6) δ 1.16 (3H, t, J=7.1 Hz), 1.96 (3H, s), 4.21 (2H, q, J=7.1 Hz), 7.28–7.33 (1H, m), 7.76–7.81 (2H, m), 9.49 (1H, br s). ^{13}C NMR (DMSO-d_6) δ 13.7, 22.9, 63.6, 112.0 (t, J_{CF}=250.1 Hz), 119.0, 128.7 (t, J_{CF}=8.4 Hz), 130.6 (t, J_{CF}=23.5 Hz), 131.7, 134.9, 135.1, 162.5 (t, J_{CF}=33.8 Hz), 169.4. ^{19}F NMR (DMSO-d_6) δ −99.5. IR 3311, 1770, 1660, 1522, 1302, 1221, 1095, 1016, 829, 654 cm^{-1}. HRMS: calcd for $C_{12}H_{12}BrF_2NO_3$ (M+H$^+$): 336.0047; found: *m*/*z* 336.0052.

*4.3.13. Ethyl 2-(2,5-dimethoxyphenyl)-2,2-difluoroacetate (**13a**).* Colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.31 (3H, t, J=7.1 Hz), 3.76 (3H, s), 3.81 (3H, s), 4.33 (2H, q, J=7.1 Hz), 6.86–6.90 (1H, m), 6.96–7.00 (1H, m), 7.19–7.21 (1H, m). ^{13}C NMR ($CDCl_3$) δ 13.8, 55.7, 56.3, 62.6, 111.8 (t, J_{CF}=7.7 Hz), 112.0 (t, J_{CF}=248.6 Hz), 112.9, 117.3, 122.7(t, J_{CF}=23.9 Hz), 150.7(t, J_{CF}=5.1 Hz), 153.5, 163.8(t, J_{CF}=33.8 Hz). ^{19}F NMR (DMSO-d_6) δ −101.0. IR 1774, 1502, 1281, 1211, 1101, 1082, 1041, 1018, 812, 715 cm^{-1}. HRMS: calcd for $C_{12}H_{14}F_2O_4$ (M+H$^+$): 261.0938; found: *m*/*z* 261.0919.

*4.3.14. Ethyl (2,4-dioxo-1,2,3,4-tetrahydropyrinidine-5-yl)difluoroacetate (**14a**).* White solid. Mp 211 °C (dec). ^{1}H NMR (DMSO-d_6) δ 1.20 (3H, t, J=7.1 Hz), 4.25 (2H, q, J=7.1 Hz), 7.29 (1H, s), 11.52 (1H, br s), 11.57 (1H, br s). ^{13}C NMR (DMSO-d_6) δ 13.8, 63.1, 105.6 (t, J_{CF}=25.0 Hz), 111.7 (t, J_{CF}=246.3 Hz), 142.6 (t, J_{CF}=7.4 Hz), 150.9, 161.7 (t, J_{CF}=4.3 Hz), 162.4 (t, J_{CF}=33.7 Hz). ^{19}F NMR (DMSO-d_6) δ −102.9. IR 3109, 2999, 2933, 1751, 1645, 1516, 1448, 1315, 1284, 1074, 1020, 777, 677 cm^{-1}. HRMS: calcd for $C_8H_8F_2N_2O_4$ (M+H$^+$): 235.0530; found: *m*/*z* 235.0513.

*4.3.15. Ethyl 2-(2-amino-3,5-dichlorophenyl)-2,2-difluoroacetate (**15a**).* Pale yellow oil. ^{1}H NMR (DMSO-d_6) δ 1.22 (3H, t, J=7.1 Hz), 4.33 (2H, q, J=7.1 Hz), 5.43 (2H, br s), 7.28–7.31 (1H, m), 7.63–7.66 (1H, m). ^{13}C NMR (DMSO-d_6) δ 13.7, 64.0, 113.0 (t, J_{CF}=251.8 Hz), 117.0 (t, J_{CF}=24.3 Hz), 119.7, 120.7, 124.8 (t, J_{CF}=8.8 Hz), 131.8, 141.1 (t, J_{CF}=2.9 Hz), 162.6 (t, J_{CF}=34.5 Hz). ^{19}F NMR (DMSO-d_6) δ −103.1. IR 3496, 3404, 1759, 1626, 1466, 1230, 1093, 1026, 868, 762, 694 cm^{-1}. HRMS: calcd for $C_{10}H_9Cl_2F_2NO_2$ (M+H$^+$): 284.0057; found: *m*/*z* 284.0063.

*4.3.16. Ethyl 2-(2-amino-3-bromo-5-methylphenyl)-2,2-difluoroacetate (**16a**).* Pale yellow oil. ^{1}H NMR (DMSO-d_6) δ 1.21 (3H, t, J=7.1 Hz), 2.20 (3H, s), 4.31 (2H, q, J=7.1 Hz), 4.96 (2H, br s), 7.13–7.16 (1H, m), 7.46–7.49 (1H, m). ^{13}C NMR (DMSO-d_6) δ 13.8, 19.5, 63.7, 110.6, 113.8 (t, J_{CF}=250.6 Hz), 116.4 (t, J_{CF}=23.5 Hz), 126.1 (t, J_{CF}=8.1 Hz), 127.1, 136.0, 143.0 (t, J_{CF}=2.9 Hz), 163.2 (t, J_{CF}=34.8 Hz). ^{19}F NMR (DMSO-d_6) δ −102.6. IR 3491, 3394, 1759, 1628, 1479, 1298, 1257, 1092, 1038, 866, 748, 700 cm^{-1}. HRMS: calcd for $C_{11}H_{12}BrF_2NO_2$ (M+H$^+$): 308.0098; found: *m*/*z* 308.0104.

*4.3.17. Ethyl 2-(2-amino-4-ethoxycarbonylphenyl)-2,2-difluoroacetate (**17a**).* Pale yellow solid. Mp 80.5–82.3 °C. ^{1}H NMR (DMSO-d_6) δ 1.23 (3H, t, J=7.1 Hz), 1.27 (3H, t, J=7.1 Hz), 4.23 (2H, q, J=7.1 Hz), 4.33 (2H, q, J=7.1 Hz), 6.08 (2H, br s), 6.81–6.85 (1H, m), 7.74–7.81 (2H, m). ^{13}C NMR (DMSO-d_6) δ 13.8, 14.4, 60.3, 63.7, 112.9 (t, J_{CF}=24.1 Hz), 114.3 (t, J_{CF}=250.3 Hz), 116.5, 116.7, 128.4 (t, J_{CF}=8.2 Hz), 133.2, 150.4, 163.2 (t, J_{CF}=35.0 Hz), 165.2. ^{19}F NMR (DMSO-d_6) δ −103.0. IR 3469, 3367, 1751, 1697, 1649, 1614, 1510, 1369, 1288, 1271, 1227, 1093, 1016, 758, 675 cm^{-1}. HRMS: calcd for $C_{13}H_{15}F_2NO_4$ (M+H$^+$): 288.1047; found: *m*/*z* 288.1059.

*4.3.18. Ethyl 2-(4-acetyl-2-aminophenyl)-2,2-difluoroacetate (**18a**).* Pale yellow solid. Mp 93.5–95.0 °C. ^{1}H NMR (DMSO-d_6) δ 1.23 (3H, t, J=7.1 Hz), 2.43 (3H, s), 4.32 (2H, q, J=7.1 Hz), 6.11 (2H, br s), 6.80–6.85 (1H, m), 7.77–7.84 (2H, m). ^{13}C NMR (DMSO-d_6) δ 13.8, 26.0, 63.7, 112.9 (t, J_{CF}=24.1 Hz), 114.3 (t, J_{CF}=250.3 Hz), 116.2, 125.0, 127.6 (t, J_{CF}=8.0 Hz), 132.8, 150.5, 163.3 (t, J_{CF}=35.1 Hz), 195.0. ^{19}F NMR (DMSO-d_6) δ −102.8. IR 3475, 3357, 1749, 1649, 1593, 1510, 1360, 1290, 1219, 1072, 1018, 823, 613 cm^{-1}. HRMS: calcd for $C_{12}H_{13}F_2NO_3$ (M+H$^+$): 258.0942; found: *m*/*z* 258.0939.

*4.3.19. Ethyl 2-(2-amino-4-cyanophenyl)-2,2-difluoroacetate (**19a**).* Pale yellow oil. ^{1}H NMR (DMSO-d_6) δ 1.22 (3H, t, J=7.1 Hz), 4.32 (2H, q, J=7.1 Hz), 6.24 (2H, br s), 6.84–6.89 (1H, m), 7.55–7.62 (2H, m). ^{13}C NMR (DMSO-d_6) δ 13.8, 63.9, 96.8, 113.6 (t, J_{CF}=250.9 Hz), 113.7 (t, J_{CF}=24.4 Hz), 117.2, 119.5, 131.3 (t, J_{CF}=8.4 Hz), 135.5, 150.1, 162.8 (t, J_{CF}=34.8 Hz). ^{19}F NMR (DMSO-d_6) δ −103.1. IR 3492, 3384, 2222, 1755, 1635, 1614, 1506, 1304, 1257, 1095, 1022, 829 cm^{-1}. HRMS: calcd for $C_{11}H_{10}F_2N_2O_2$ (M+H$^+$): 241.0789; found: *m*/*z* 241.0786.

*4.3.20. 5,7-Dichloro-3,3-difluoro-2,3-dihydroindole-2-one (**15b**).* Pale yellow solid. Mp 145 °C (dec). ^{1}H NMR (DMSO-d_6) δ 7.80–7.83 (1H, m), 7.86–7.89 (1H, m), 11.83 (1H, br s). ^{13}C NMR (DMSO-d_6) δ 110.5 (t, J_{CF}=250.9 Hz), 117.1, 122.1 (t, J_{CF}=23.5 Hz), 124.2, 128.1, 133.5, 139.8 (t, J_{CF}=7.5 Hz), 165.7 (t, J_{CF}=29.1 Hz). ^{19}F NMR (DMSO-d_6) δ −110.6. IR 3197, 1761, 1624, 1464, 1271, 1188, 1092, 874, 837, 737, 700 cm^{-1}. HRMS: calcd for $C_8H_3Cl_2F_2NO$ (M−H$^+$): 235.9481; found: *m*/*z* 235.9506.

*4.3.21. 7-Bromo-3,3-difluoro-2,3-dihydro-5-methylindole-2-one (**16b**).* Pale yellow solid. Mp 139 °C (dec). ^{1}H NMR (DMSO-d_6) δ 2.29 (3H, s), 7.51 (1H, s), 7.57 (1H, s), 11.42 (1H, br s). ^{13}C NMR (DMSO-d_6) δ 20.1, 103.8, 111.4 (t, J_{CF}=249.5 Hz), 121.0 (t, J_{CF}=23.1 Hz), 124.7, 135.1, 136.9, 139.6 (t, J_{CF}=7.6 Hz), 166.0 (t, J_{CF}=29.3 Hz). ^{19}F NMR (DMSO-d_6) δ −110.1. IR 3192, 1761, 1626, 1481, 1298, 1192, 1080, 1036, 791, 762, 737, 696 cm^{-1}. HRMS: $C_9H_7F_2NOBr$ (M+H$^+$): 261.9679; found: *m*/*z* 261.9702.

*4.3.22. Ethyl 3,3-difluoro-2-oxo-2,3-dihydro-1H-indole-5-carboxylate (**17b**).* Pale yellow solid. Mp 176 °C (dec). ^{1}H NMR (DMSO-d_6) δ 1.31 (3H, t, J=7.1 Hz), 4.30 (2H, q, J=7.1 Hz), 7.09–7.13 (1H, m), 8.10–8.14 (2H, m), 11.59 (1H, br s). ^{13}C NMR (DMSO-d_6) δ 14.2, 61.1, 110.7 (t, J_{CF}=249.5 Hz), 112.1, 119.6 (t, J_{CF}=23.1 Hz), 125.1, 125.6, 135.9, 147.0 (t, J_{CF}=7.3 Hz), 164.7, 166.1 (t, J_{CF}=29.4 Hz). ^{19}F NMR (DMSO-d_6) δ −111.6. IR 3296, 1768, 1739, 1705, 1631, 1240, 1203,

1080, 760, 739, 660, 611 cm^{-1}. HRMS: calcd for $C_{11}H_9F_2NO_3$ ($M+H^+$): 242.0629; found: *m*/*z* 242.0627.

*4.3.23. 5-Acetyl-3,3-difluoro-2,3-dihydroindole-2-one (**18b**).* Pale yellow solid. Mp 208 °C (dec). ^1H NMR (DMSO-d_6) δ 2.55 (3H, s), 7.08 (1H, d, *J*=8.3 Hz), 8.11 (1H, d, *J*=8.3 Hz), 8.19 (1H, s), 11.57 (1H, br s). ^{13}C NMR (DMSO-d_6) δ 26.7, 110.9 (t, J_{CF}=249.5 Hz), 112.0, 119.6 (t, J_{CF}=23.0 Hz), 125.2, 132.5, 135.1, 146.9 (t, J_{CF}=7.3 Hz), 166.3 (t, J_{CF}=29.4 Hz), 196.1. ^{19}F NMR (DMSO-d_6) δ −111.5. IR 3159, 1766, 1670, 1620, 1362, 1240, 1203, 1109, 1082, 928, 837, 660 cm^{-1}. HRMS: calcd for $C_{10}H_7F_2NO_2$ ($M+H^+$): 212.0523; found: *m*/*z* 212.0502.

*4.3.24. 3,3-Difluoro-2-oxo-2,3-dihydro-1H-indole-5-carbonitrile (**19b**).* White solid. Mp 241 °C (dec). ^1H NMR (DMSO-d_6) δ 7.13 (1H, d, *J*=8.3 Hz), 7.97 (1H, d, *J*=8.3 Hz), 8.25 (1H, s), 11.68 (1H, br s). ^{13}C NMR (DMSO-d_6) δ 105.9, 110.2 (t, J_{CF}=250.3 Hz), 113.1, 118.4, 120.3 (t, J_{CF}=23.3 Hz), 129.3, 139.3, 147.0 (t, J_{CF}=7.3 Hz), 165.8 (t, J_{CF}=29.2 Hz). ^{19}F NMR (DMSO-d_6) δ −111.8. IR 3211, 2229, 1778, 1745, 1626, 1487, 1296, 1223, 1178, 1095, 843, 768, 665 cm^{-1}. HRMS: calcd for $C_9H_4F_2N_2O$ ($M+H^+$): 195.0370; found: *m*/*z* 195.0379.

*4.3.25. 5-Chloro-3,3-difluoro-2,3-dihydroindole-2-one (**20b**).* Pale yellow solid. Mp 188 °C (dec). ^1H NMR (DMSO-d_6) δ 6.98–7.02 (1H, m), 7.55–7.59 (1H, m), 7.81–7.84 (1H, m), 11.31 (1H, br s). ^{13}C NMR (DMSO-d_6) δ 110.8 (t, J_{CF}=250.0 Hz), 113.7, 121.0 (t, J_{CF}=23.0 Hz), 125.3, 127.5, 134.2, 141.6 (t, J_{CF}=7.6 Hz), 165.6 (t, J_{CF}=29.2 Hz). ^{19}F NMR (DMSO-d_6) δ −111.4. IR 3207, 1774, 1730, 1622, 1481, 1456, 1271, 1221, 1205, 1090, 833, 762, 710, 660, 617 cm^{-1}. HRMS: calcd for $C_8H_4F_2NOCl$ ($M-H^+$): 201.9871; found: *m*/*z* 201.9903.

*4.3.26. 3,3-Difluoro-2,3-dihydroindole-5-nitro-2-one (**21b**).* Pale yellow solid. ^1H NMR (DMSO-d_6) δ 7.16–7.21 (1H, m), 8.39–8.44 (1H, m), 8.54–8.58 (1H, m), 11.86 (1H, br s). ^{13}C NMR (DMSO-d_6) δ 108.1 (t, J_{CF}=250.7 Hz), 112.7, 119.9 (t, J_{CF}=23.4 Hz), 121.2, 130.8, 143.4, 148.8 (t, J_{CF}=7.3 Hz), 166.1 (t, J_{CF}=29.2 Hz). ^{19}F NMR (DMSO-d_6) δ −111.9. EI-MS: calcd for $C_8H_4F_2N_2O_3$ (M): 214.019; found: *m*/*z* 214. Full characterization is shown in Ref. 17.

*4.3.27. 3,3-Difluoro-2,3-dihydro-1,5-dimethylindole-2-one (**22b**).* White solid. Mp 85.8–88.0 °C. ^1H NMR (DMSO-d_6) δ 2.32 (3H, s), 3.14 (3H, s), 7.10 (1H, d, *J*=8.0 Hz), 7.41 (1H, d, *J*=8.0 Hz), 7.51 (1H, s). ^{13}C NMR (DMSO-d_6) δ 20.4, 26.4, 110.6, 111.5 (t, J_{CF}=248.0, 118.9 (t, J_{CF}=22.6, 124.9, 133.6, 134.4, 141.7 (t, J_{CF}=7.4), 164.4 (t, J_{CF}=30.0). ^{19}F NMR (DMSO-d_6) δ −111.2. IR 1741, 1626, 1504, 1493, 1298, 1250, 1115, 1068, 1012, 825, 737, 714 cm^{-1}. HRMS: calcd for $C_{10}H_9F_2NO$ ($M+H^+$): 198.0725; found: *m*/*z* 198.0705.

*4.3.28. 5-Chloro-3,3-difluoro-1,3-dihydropyrrolo[2,3-b]pyridine-2-one (**23b**).* White solid. Mp 189 °C (dec). ^1H NMR (DMSO-d_6) δ 8.38–8.41 (1H, m), 8.44–8.47 (1H, m), 12.07 (1H, br s). ^{13}C NMR (DMSO-d_6) δ 110.4 (t, J_{CF}=252.2 Hz), 115.3 (t, J_{CF}=23.5 Hz), 126.0, 134.0, 151.1, 155.9 (t, J_{CF}=7.8 Hz), 165.8 (t, J_{CF}=28.8 Hz). IR 3051, 1772, 1622, 1456, 1284, 1188, 1086, 951, 918, 750, 667, 615 cm^{-1}. ^{19}F NMR (DMSO-d_6) δ −112.0. HRMS: calcd for $C_7H_3ClF_2N_2O$ ($M-H^+$): 202.9824; found: 202.9810.

References and notes

1. Bégué, J.-P.; Bonnet-Delpon, D. *Bioorganic and Medicinal Chemistry of Fluorine*; Wiley: Hoboken, 2008.
2. Boechat, N.; Kover, W. B.; Bastos, M. M.; Pinto, A. C.; Maciel, L. C.; Mayer, L. M. U.; da Silva, F. S. Q.; Sá, P. M.; Mendonça, J. S.; Wardella, S. M. S. V.; Arruda, M. S. L. *J. Braz. Chem. Soc.* **2008**, *19*, 445.
3. (a) Young, R. N.; Billot, X.; Han, Y.; Slipetz, D. A.; Chauret, N.; Belley, M.; Metters, K.; Mathieu, M.-C.; Greig, G. M.; Denis, D.; Girard, M. *Heterocycles* **2004**, *64*, 437; (b) Eto, H.; Kaneko, Y.; Sakamoto, T. *Chem. Pharm. Bull.* **2000**, *48*, 982.
4. Middleton, W. J.; Bingham, E. M. *J. Org. Chem.* **1980**, *45*, 2883.
5. Fauq, A. H. In *N,N-Deiethylaminosulfur Trifluoride*; Paquette, L., Ed.; John Wiley & Sons: New York, NY, 2004.
6. (a) Sato, K.; Kawata, R.; Ama, F.; Omote, M.; Ando, A.; Kumadaki, I. *Chem. Pharm. Bull.* **1999**, *47*, 1013; (b) Sato, K.; Omote, M.; Ando, A.; Kumadaki, I. *J. Fluorine Chem.* **2004**, *125*, 509.
7. (a) Murakami, S.; Kim, S.; Ichii, H.; Fuchigami, T. *Synlett* **2004**, 815; (b) Murakami, S.; Ishi, H.; Tajima, T.; Fuchigami, T. *Tetrahedron* **2006**, *62*, 3761.
8. Huang, X.-T.; Long, Z.-Y.; Chen, Q.-Y. *J. Fluorine Chem.* **2001**, *11*, 107.
9. (a) Uraguchi, D.; Yamamoto, K.; Otsuka, Y.; Tokuhisa, K.; Yamakawa, T. *Appl. Catal., A* **2008**, *342*, 137; (b) Kino, T.; Nagase, Y.; Uraguchi, D.; Yamamoto, K.; Otsuka, Y.; Tokuhisa, T.; Yamakawa, T. *J. Fluorine Chem.* **2010**, *131*, 98.
10. Goldstein, S.; Meyerstein, D.; Czapkj, G. *Free Radical Biol. Med.* **1993**, *15*, 435.
11. (a) Eicher, T.; Hauptmann, S. *Chemistry of Heterocycles*; Wiley: Weinheim, 2003; (b) Katrizsky, A.-R.; Fan, W.-Q. *Heterocycles* **1992**, *34*, 2179.
12. (a) Logan, S. R. *Can. J. Chem.* **1991**, *69*, 540; (b) Li, L.; Shi, J.; Yao, Y.-J.; Zhao, X.; Chen, H. *Appl. Catal., A* **2004**, *263*, 213; (c) Ishio, M.; Terashima, T.; Ouchi, M.; Sawamoto, M. *Polym. J.* **2010**, *42*, 17; (d) Reger, D. L.; Mintz, E.; Lebioda, L. *J. Am. Chem. Soc.* **1986**, *108*, 1940; (e) Fürstner, A.; Majima, K.; Martin, R.; Krause, H.; Kattnig, G.; Goddard, R.; Lehmann, C. W. *J. Am. Chem. Soc.* **2008**, *130*, 1992; (f) Fürstner, A.; Martin, R.; Krause, H.; Seidel, G.; Goddard, R.; Lehmann, C. W. *J. Am. Chem. Soc.* **2008**, *130*, 8773.
13. With regard to entries 6 and 7, the tautmeric isomers should be taken into account. On the basis of the electron density, the ethoxycarbonyldifluoromethylated positions will be the 3- and 4-position of the isomers of 4-methylpyrazole and 4-phenylimidazole, respectively. These positions correspond to the 2-position of 4-methylpyrazole and 4-phenylimidazole. Thus, it can be concluded that the same discussion on the electrophilic substitution is applied to the tautmeric isomers.
14. In the reaction solution of benzo[*b*]furane, some very small peaks other than **5a** were detected by ^{19}F NMR. These peaks may be assigned to the products, which the each phenyl ring was ethoxycarbonyldifluoromethylated. Since the formed amounts of these products were very small, they were not characterized.
15. Roth, G. J.; Heckel, A.; Colbatzky, F.; Handschuh, S.; Kely, J.; Lehmann-Lintz, T.; Lotz, R.; Tontsch-Grunt, U.; Ealter, R.; Hilberg, F. *J. Med. Chem.* **2009**, *52*, 4466.
16. Özcan, S.; Malci, M. *Tetrahedron* **2008**, *64*, 5531.
17. Poel, T.-J. WO2004/074282.Starck, J.-P. WO2006/008067.
18. Torres, J. C.; Garden, S. J.; Pinto, A. C.; de Silva, F. S. Q.; Boechat, N. *Tetrahedron* **1999**, *55*, 1881.
19. (a) Marvel, C. S.; Hiers, G. S. In *Organic Syntheses Collective*, Second Edition; Gilman, H., Ed.; John Wiley & Sons: New York, NY, 1964; Vol. I, p 327; (b) Lackey, K.; Sternbach, D. D. *Synthesis* **1993**, 993; (c) Smith, K.; El-Hiti, G. A.; Hawes, A. C. *Synlett* **1999**, 945.