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A Two-Step Sequence to Ethyl α-Fluorocyclopropanecarboxylates Through MIRC Reaction of Ethyl Dichloroacetate and Highly Regioselective Fluorination

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A two-step sequence to ethyl α-fluorocyclopropanecarboxylates has been developed. Ethyl α-chlorocyclopropanecarboxylates were first obtained through a Michael-initiated ring closure reaction of terminal electron-deficient olefins with ethyl 2,2-dichloroacetate under mild basic conditions. Subsequent smooth conversion into the corresponding monofluorinated analogues in good yields was through a halogen exchange reaction with potassium bifluoride. Further investigation clearly demonstrated that potassium bifluoride in this reaction system played a dual role of base and nucleophilic reagent. This is the first successful example reported hitherto for producing ethyl α-fluorocyclopropanecarboxylate directly through fluorination of its chlorinated analogue with alkali bifluoride.

Introduction

Cyclopropyl groups are found as a basic structural element in a lot of biologically and pharmacologically active substances.[1,2] Introduction of the cyclopropane moiety into biologically active substances has been recognized as an important chemical modification owing to its conformational rigidity and potential chemical reactivity.[3] Moreover, various cyclopropane-containing unnatural products have been prepared and used as versatile intermediates in the synthesis of more functionalized cyclic and acyclic compounds.[4]

Owing to its unique properties – high electronegativity, stable bonds to carbon, and small atomic radius similar to that of hydrogen – fluorine is usually introduced into an organic compound to drastically modify its chemical, physical and biological properties, such as solubility, lipophilicity, conformation, and metabolic stability.[5] Today, fluorine is frequently used to modulate the properties of a potential drug by medicinal chemists, and a growing number of fluorinated drugs have found use in medical applications over the past several decades.[6] As a consequence, incorporation of fluorine into organic molecules has received considerable interest in recent years as the number of biologically active fluorinated compounds continues to grow.[7]

Fluorinated cyclopropanes, which combine both the unique properties of cyclopropane and fluorine, can be envisioned as new powerful scaffolds for building new bioactive molecules and therapeutic agents.[8] Among them, monofluorinated cyclopropanes have received considerable attention over recent years owing to their attractive biological activities, examples of which include monoamine oxidase inhibitors, nitric oxide synthase inhibitors, antivirals, antibacterial agents, and mGluR inhibitors for the treatment of neurological disorders.[9]

Synthetic methods of monofluorinated cyclopropanes[9] reported previously mainly include [2+1] cycloaddition of fluorocarbenes to olefins, [2+1] cycloaddition of carbenes to fluoroalkenes, radical addition of ethyl iodofluoroacetate with subsequent intramolecular nucleophilic substitution, and direct fluorination with 5% F_2/N_2. Recently, Michael-initiated ring closure (MIRC) reactions have been successfully applied to synthesize monofluorinated cyclopropane compounds. Jubault et al.[10] reported the reaction of ethyl dibromofluoroacetate with electron-deficient olefins in the presence of diethylzinc or Zn/LiCl, and Hu et al.[11] developed the first chiral monofluoromethylenation reagent, (*R*)-*N*-tosyl-*S*-fluoromethyl-S-phenylsulfoximine, for the synthesis of chiral monofluorinated cyclopropanes. Very recently, Charette et al.[12] reported the highly enantioselective Simmons-Smith fluorocyclopropanation of allylic alcohols by using difluoroiodomethane and ethylzinc iodide as the substituted carbenoid precursors. Although the utility of existing methods was demonstrated by the synthesis of several types of biologically active compounds, the fluorine sources they used are rather limited. Therefore, it is still interesting for us to develop mild and practical methods for constructing monofluorinated cyclopropanes. Herein, we

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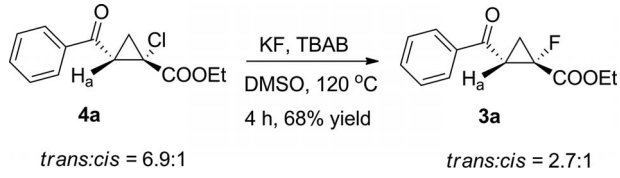
present a practical synthetic route of ethyl α-fluorocyclopropanecarboxylates by using KF or KHF_2 as the fluorine sources.

Results and Discussion

According to the MIRC reaction pattern, we tried to obtain ethyl α-fluorocyclopropanecarboxylate through the reaction of ethyl bromofluoroacetate (**1a**) with 1-phenyl-2-propenone (**2a**) in the presence of Cs_2CO_3 in dimethylformamide (DMF). Unfortunately, no desired product ethyl 2-benzoyl-1-fluorocyclopropanecarboxylate (**3a**) was detected during this reaction even after various bases and solvents were screened (Scheme 1). Further investigation demonstrated that **1a** was easily hydrolyzed into ethyl glyoxalate under these reaction conditions, indicating that the failure of the MIRC reaction for **1a** could be attributed to the facile elimination of bromide from its conjugate base.

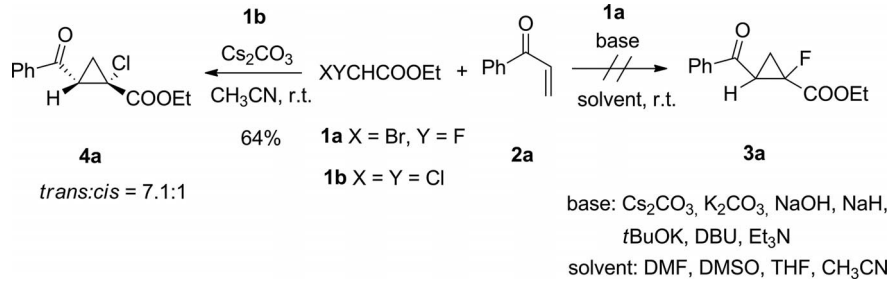
To understand the effect of halogen properties well, ethyl dichloroacetate (**1b**), a commercially available reagent, was used and assessed. Pleasingly, its reaction with **2a** in acetonitrile took place smoothly in the presence of Cs_2CO_3 at room temperature, giving ethyl α-chlorocyclopropanecarboxylate (**4a**) in 64% yield (Scheme 1). Its steric structure was characterized by the heteronuclear single quantum correlation (HSQC) and the heteronuclear multiple bond correlation (HMBC) experiments, and the main isomer was assigned to be of *trans*-configuration.[13]

With monochlorinated cyclopropane **4a** in hand, the problem we faced was how to convert **4a** into fluorinated analogue **3a**. The common fluorination of chlorinated compounds, except the direct substitution through an S_N2 reaction, is usually achieved by using anhydrous HF and fluorinated Lewis acids such as SbF_3 or SbF_5 as the fluorinating reagents.[14] Considering the instability of cyclopropane to strong acids, we conducted a preliminary experiment with KF as the fluorine source, dimethyl sulfoxide (DMSO) as the solvent and 20 mol-% of tetrabutyl ammonium bromide (TBAB) as the phase-transfer catalyst at 120 °C. As a consequence, compound **4a** disappeared completely within four hours, and a new compound was generated with slightly higher polarity than **4a** through TLC detection (Scheme 2). Gratifyingly, further spectroscopic characterization of the newly formed compound by ^1H, ^{13}C and ^{19}F NMR spectroscopy demonstrated that it was desired fluorinated products *trans*/*cis*-**3a**, which were inseparable by silica-gel column chromatography. Based on the Karplus equation, *trans*-**3a** was easily distinguished from *cis*-**3a** from their different splitting constants $J_{Ha\text{-}F}$ (2.7 Hz for the *trans* isomer, and 18.7 Hz for the *cis* isomer) owing to their different dihedral angles.[10a,15] This assignment was further confirmed by HSQC and HMBC experiments. To the best of our knowledge, this is the first successful example related to synthesis of ethyl α-fluorocyclopropanecarboxylates from its chlorinated analogues.



Scheme 2. Fluorination of monochlorinated cyclopropane **4a**.

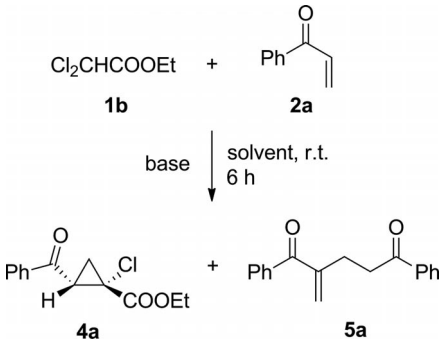
Encouraged by these preliminary results, we turned our attention to evaluate the reaction parameters and the substrate scope suitable for this reaction. The MIRC reaction between ethyl dichloroacetate **1b** and the enone **2a** was chosen as the model reaction to optimize the reaction conditions including the base and solvent at room temperature. All the results are summarized in Table 1. The reaction proceeded smoothly in the presence of Cs_2CO_3 with acetonitrile as the solvent (Table 1, Entry 1). Potassium carbonate, a common inorganic base, can readily promote the reaction at room temperature, but provided desired product **4a** only in 16% yield with 4.8:1 *dr* value (Table 1, Entry 2). Strong base such as NaOH afforded product **4a** only in 9% yield (Table 1, Entry 3). Much stronger bases, NaH, EtONa and *t*BuOK were inferior for this reaction (Table 1, Entries 4, 6, 7), in which NaH could lead to further decomposition of **4a**, and EtONa or *t*BuOK preferred to add to enone **2a**. Another common base, tetrabutylammonium fluoride (TBAF) also gave **4a** in a low yield (Table 1, Entry 5). Organic bases such as 1,4-diazabicyclo[2.2.2]octane (DABCO) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in this reaction always caused oligomerization or a Rauhut-Currier (RC) side-reaction[16] of **2a** and gave a certain amount of oligomer or self-dimer **5a** (Table 1, Entries 8–11). Therefore, Cs_2CO_3 was the most promising base for this MIRC reaction. Next, a group of solvents were further assessed. Strong aprotic polar solvents commonly favored



Scheme 1. Reaction between ethyl dihaloacetate and 1-phenyl-2-propenone (**2a**).

the formation of **4a** (Table 1, Entries 12–13), and the isolated yield reached 71% in DMF. However, the use of tetrahydrofuran (THF) and 1,4-dioxane resulted in a significant decrease in the chemical yield, and almost no desired product was isolated (Table 1, Entries 14–15).

Table 1. Optimization of the MIRC reaction between **1b** and **2a**.[a]

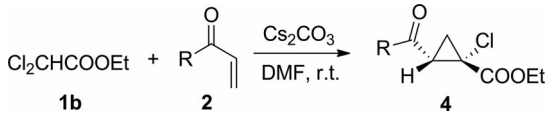


Entry	Base	Solvent	**4a** yield [%][b]	*trans*/*cis*[c]	**5a** yield [%][b]
1	Cs_2CO_3	CH_3CN	64	7.1:1	0
2	K_2CO_3	CH_3CN	16	4.8:1	0
3	NaOH	CH_3CN	9	5:1	0
4	NaH	CH_3CN	trace	–	0
5	TBAF	CH_3CN	4	4.8:1	0
6	EtONa	CH_3CN	trace	–	0
7	*t*BuOK	CH_3CN	trace	–	0
8	DABCO	CH_3CN	0	–	12
9	DBU	CH_3CN	8	4.9:1	6
10	DMAP	CH_3CN	0	–	6
11	hydroquinine	CH_3CN	0	–	trace
12	Cs_2CO_3	DMSO	67	6.9:1	0
13	Cs_2CO_3	DMF	71	7.1:1	0
14	Cs_2CO_3	THF	trace	–	0
15	Cs_2CO_3	1,4-dioxane	trace	–	0

[a] Reactions were carried out with **1b** (0.5 mmol), **2a** (0.5 mmol), and base (0.6 mmol) in solvent (2 mL) at room temperature for 6 h. [b] Isolated yields. [c] Determined by ^{1}H NMR spectroscopy of the crude product.

Under the optimized reaction conditions, the diversity of electron-deficient olefins was explored, and the results are summarized in Table 2. The terminal electron-deficient olefins with a considerable degree of structure variations underwent the MIRC reaction smoothly to afford the expected products in moderate to good chemical yields with good diastereoselectivities under the specified reaction conditions. The electronic nature of the substituent on the aromatic ring did not exert any significant influence over the product yields, whereas electron-donating groups slowed down the reaction rate (Table 2, Entries 1–6, 11). Enones **2i** and **2j** with heterocyclic 2-thienyl and fused-ring 1-naphthyl groups were easily tolerated, and satisfying yields were achieved with excellent *dr* values (Table 2, Entries 9, 10). It is noteworthy that reaction of aliphatic enone, methyl vinyl ketone (MVK; **2g**), proceeded smoothly, giving corresponding product **4g** in 76% yield with a good *dr* value (Table 2, Entry 7). In contrast, cyclohexenone, a typical nonterminal enone, did not undergo the above MIRC reaction. Moreover, methyl acrylate (MA; **2h**), a less reactive Michael acceptor than MVK, worked well in this system to afford desired product **4h** in good yield and excellent *dr* value (Table 2, Entry 8), whereas methyl methacrylate gave no detectable MIRC product. The reaction of acrylamide was very slow, and gave only a little of the MIRC product. In addition, we noticed that the *trans*/*cis* ratios for **4** listed in Table 2 varied from 5.1:1 to 20:1 with the change of R group, and the diastereoselectivity for **4h** derived from methyl acrylate was the best. Finally, for the practical use of this protocol, we examined the model reaction of **1b** and **2a** on a 10.0 mmol scale (20 times larger) and the same good result was observed (Table 2, Entry 12).

Table 2. Scope of the MIRC reaction between **1b** and **2**.[a]



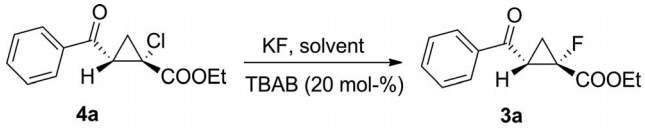
Entry	R	Product	Time [h]	Yield [%][b]	*trans*/*cis*[c]
1	C_6H_5 **2a**	**4a**	6	71	7.1:1
2	4-MeC_6H_4 **2b**	**4b**	10	70	5.1:1
3	4-MeOC_6H_4 **2c**	**4c**	10	76	6.3:1
4	4-MeSC_6H_4 **2d**	**4d**	10	60	9.1:1
5	4-ClC_6H_4 **2e**	**4e**	4	58	16.7:1
6	4-BrC_6H_4 **2f**	**4f**	4	61	15.6:1
7	Me **2g**	**4g**	6	76	9.1:1
8	MeO **2h**	**4h**	6	74	20:1
9	2-thienyl **2i**	**4i**	2	62	12.5:1
10	1-naphthyl **2j**	**4j**	5	80	16.1:1
11	4-PhC_6H_4 **2k**	**4k**	5	72	6.3:1
12[d]	C_6H_5 **2a**	**4a**	6	70	6.9:1

[a] Reactions were carried out with **1b** (0.5 mmol), **2** (0.5 mmol) and Cs_2CO_3 (0.6 mmol) in DMF (2 mL) at room temperature for the given time. [b] Isolated yields. [c] Determined by ^{1}H NMR spectroscopy of the crude product. [d] Reaction on a 10.0 mmol scale of **2a**.

Because chlorinated products **4a**–**4k** could be conveniently obtained through the MIRC process, next we turned our attention to the optimization of fluorination reaction conditions of these compounds. The reaction parameters including solvents, reaction temperature and amount of KF, were screened by choosing the reaction of **4a** as the model. The results are described in Table 3. As mentioned above, KF smoothly converted **4a** into fluorinated analogue **3a** in DMSO at 120 °C in 68% yield (Table 3, Entry 1). Further experiments showed that the reaction temperature had a significant influence on the reaction (Table 3, Entries 2–5). At room temperature, the reaction did not take place at all. When the temperature was elevated to 80 °C, the reaction proceeded slowly, and only 55% of substrate **4a** was converted after 48 h. The reaction was markedly accelerated when the reaction temperature was raised to 100 °C. A slight decrease in the yield was observed when the reaction temperature was further elevated to 140 °C, although substrate **4a** was consumed completely in 2 h (Table 3, Entry 5). Obviously, a temperature higher than 100 °C was crucial to this reaction, but too high a temperature is not beneficial. Thus, the following experiments were performed at 120 °C. DMSO turned out to be the promising solvent employed in

this reaction (Table 3, Entries 1, 6–7). The amount of KF used also influenced the reaction (Table 3, Entries 1, 8–9). One equivalent of KF did not convert **4a** completely, and gave only 48% yield of desired product **3a**. However, no improvement in yield was observed when three equivalents of KF were used. Stereochemical analysis of the products clearly indicated there was an obvious decline in the diastereoselectivity from 6.9:1 (*dr* for **4a**) to 2.7:1 (*dr* for **3a**; Table 3, Entry 1) during the fluorination process, although *trans*-**3a** remained the main isomer.

Table 3. Optimization of the fluorination reaction of **4a** with KF.[a]



4a **3a**

trans:*cis* = 6.9:1

Entry	Solvent	*T* [°C]	Time [h]	Conv. [%]	Yield [%][b]	*trans*/*cis*[c]
1	DMSO	120	4	100	68	2.7:1
2	DMSO	r. t.	26	0	0	–
3	DMSO	80	48	55	69(38)	1.6:1
4	DMSO	100	20	90	62(56)	2.4:1
5	DMSO	140	2	100	55	2.4:1
6	DMF	120	2	100	34	2.2:1
7	PEG400	120	4	100	0	–
8[d]	DMSO	120	4	90	48(43)	1.8:1
9[e]	DMSO	120	4	100	68	2.5:1

[a] Reactions were carried out with **4a** (0.5 mmol), KF (2 equiv. unless otherwise stated), TBAB (20 mol-%) in solvent (2 mL) at the given temperature. [b] Yields based on converted **4a**, and isolated yields in parentheses. [c] Determined by ^{1}H NMR spectroscopy of the crude product. [d] KF (1 equiv.) was used. [e] KF (3 equiv.) was used.

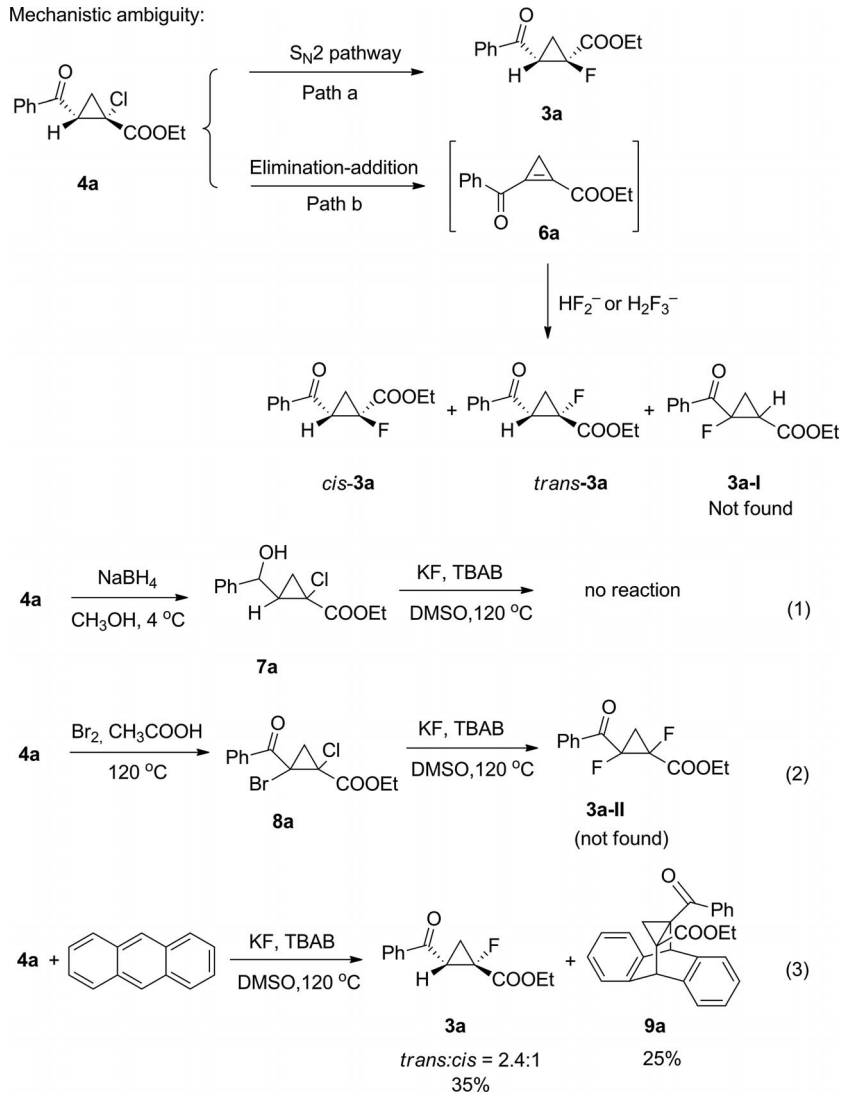
The effect of different fluorine sources on the above reaction was also investigated. Two common, commercially available, fluorine reagents CsF and KHF_2 were utilized in the following assessment. The results are summarized in Table 4. Moderately basic CsF smoothly converted **4a** into fluorinated analogue **3a** in DMSO at 120 °C within 2 h in 40% yield (Table 4, Entry 1). In contrast, potassium bifluoride (KHF_2), a weakly acidic reagent, gave a much higher yield of **3a** under the same conditions despite a prolonged required reaction time (Table 4, Entry 2). From the above observations, we were aware of a significant effect of the basicity for the fluorine source on the reaction. Thus, we estimated the influence of basic K_2CO_3 on the reaction, and found its addition can markedly accelerate the consumption rate of **4a**, but disfavored formation of **3a** (Table 4, Entry 3). Moreover, the yield of **3a** would be further decreased with extended reaction times (Table 4, Entry 4). These results indicate that fluorinated product **3a** was not very stable and decomposed slowly during the reaction under basic conditions. The side products formed were highly polar and hardly moved up on a TLC plate [mobile phase: petroleum/ethyl acetate, 10:1 (v/v)]. The same trend in the conversion ratio of **4a** and in yield of **3a** was also found during the reaction in the absence of K_2CO_3 (Table 4, Entries 5–8). Based on the yields observed (Table 4, Entries 2 and 8), the addition of TBAB as the phase-transfer catalyst seems unnecessary for this reaction. In the absence of TBAB, the fluorination reaction of **4a** with KHF_2 was smooth at 120 °C, and gave **3a** in 75% yield after 12 h. The temperature and solvent also have great influence on this reaction, and the details are given in the Supporting Information. The dose of KHF_2 also had some effect on the reaction, and the best result was obtained by using three equivalents of KHF_2 (Table 4, Entries 9–11). Thus, the optimized conditions for the fluorination reaction were ascertained: KHF_2 (3 equiv.) as the fluorine source and DMSO as the solvent at 120 °C. It should be noted that there was no marked effect on the diastereoselectivity of fluorination process by the fluorine sources, and the *trans*/*cis* ratios changed from 2.0:1 to 2.6:1.

Table 4. Optimization of fluorination of **4a** with other fluorine sources.[a]

Entry	Fluorine source	*T* [°C]	Time [h]	Conv. [%]	Yield [%][b]	*trans*/*cis*[c]
1[d]	CsF	120	2	100	40	2.4:1
2[d]	KHF_2	120	12	100	74	2.3:1
3[e]	KHF_2	120	2	80	25 (20)	2.2:1
4[e]	KHF_2	120	4	100	8	2.0:1
5	KHF_2	120	4	50	92 (46)	2.4:1
6	KHF_2	120	7	72	88 (64)	2.6:1
7	KHF_2	120	9	95	82 (78)	2.5:1
8	KHF_2	120	12	100	75	2.4:1
9[f]	KHF_2	120	9	65	80 (52)	2.4:1
10[g]	KHF_2	120	9	95	85 (81)	2.6:1
11[h]	KHF_2	120	9	95	83 (79)	2.5:1

[a] Reactions were carried out with **4a** (0.5 mmol), fluorine source (2 equiv. unless otherwise stated) in DMSO (2 mL) at the given temperature. [b] Yields based on converted **4a**, isolated yields in parentheses. [c] Determined by ^{1}H NMR spectroscopy of the crude product. [d] TBAB (20 mol-%) was used. [e] K_2CO_3 (2 equiv.) was used. [f] KHF_2 (1 equiv.) was used. [g] KHF_2 (3 equiv.) was used. [h] KHF_2 (4 equiv.) was used.

The above observations assured us that the fluorination reaction of **4a** with KF or KHF_2 could proceed smoothly under the basic reaction conditions. However, the direct nucleophilic substitution of halogen by fluoride on a cyclopropane ring has seldom been reported.[17] According to the features of this reaction, we realized there were two possible reaction pathways. One possibility is that both the electron-withdrawing carbonyl group and ester group on the cyclopropane ring of **4a** might weaken the C–Cl bond together, which would make the direct nucleophilic fluorination smooth. Another possibility would be that the existence of an acidic α-H of the carbonyl group for **4a** leads to facile elimination of HCl, and then the generated cyclopropene intermediate **6a** combined regioselectively with HF_2^- or $H_2F_3^-$ generated in situ to afford fluorinated product **3a** (Scheme 3).[18] Namely, the mechanistic ambiguity lies in whether the reaction would undergo along the common S_N2 route or along an elimination/addition route. To solve



Scheme 3. Mechanistic investigation for the fluorinated reaction of **4a**.

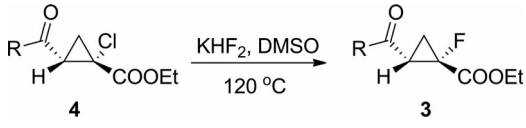
this problem, some mechanistically pertinent experiments were carried out.

Firstly, the effect of carbonyl group on the fluorinating reaction was assessed. Substrate **4a** was reduced to form alcoholic compound **7a** with sodium borohydride, which was then treated with KF under the fluorinating conditions mentioned above. No fluorination reaction occurred at all in this case [Scheme 3, Equation (1)]. This result indicated that a carbonyl group was vital to the fluorination process of **4a**. Next, the role of the acidic α-H of **4a** was examined. The acidic α-H of **4a** was blocked through bromination in anhydrous acetic acid, and then the generated **8a** was treated under the above fluorinating system. To our surprise, no desired difluorinated compound **3a-II** was formed [Scheme 3, Equation (2)]. The above results show that fluorination does not proceed along a S_N2 mechanism (Scheme 3, Path a). Lastly, we tried to capture cyclopropene intermediate **6a** generated in situ possibly during the reaction by adding anthracene (2 equiv.) as a diene to the fluorinating reaction system. As we expected, the reaction afforded Diels–Alder adduct **9a** in 25% yield together with monofluorinated product **3a** in 35% yield [Scheme 3, Equation (3)]. The successful capture of cyclopropene intermediate **6a** strongly supports the opinion that fluorination proceeds through an elimination/addition route (Scheme 3, Path b). Moreover, the experimental observations assured us that the addition of **6a** with HF_2^- or $H_2F_3^-$ must be a highly regioselective process owing to no detectable formation of **3a-I**. Furthermore, this elimination/addition mechanistic proposal can rationalize why the original diastereoselectivity for **4a** disappeared during the fluorination process. In general, because the size of fluorine atom is much smaller than that of chlorine, predominant formation of *trans*-**3a** would be expected during the addition step through epimerization owing to less steric hindrance relative to *cis*-**3a**. The *dr* values for **3a** observed during the fluorination process were relatively lower than that for **4a** without exception. Although the real reason for this is still

unclear, the existence of weak H-bonding between *cis*-**3a** and the surrounding HF_2^- might be a potential factor benefitting the formation of *cis*-**3a**.

Next, various ethyl α-chlorocyclopropanecarboxylates listed in Table 2 were chosen for subsequent fluorination reaction to exploit the substrate scope under the above optimized fluorinating conditions. The results are given in Table 5. Obviously, the electronic properties of the substituent groups at the cyclopropane ring had a marked effect on the reaction. For substrates **4a**–**4f** with substituted benzoyl groups, fluorination reactions with KHF_2 gave high conversions and high yields of products **3a**–**3f** in each case (Table 5, Entries 1–5). Electron-donating *p*-methyl and *p*-methoxy groups greatly retarded the reactions and electron-withdrawing *p*-chloro and *p*-bromo groups accelerated the reactions. In contrast, conversion of **4g** with an acetyl group was very slow, and yielded little product **3h** (Table 5, Entry 6). TLC analysis clearly indicated no reaction occurred for substrates **4h** with a methoxycarbonyl group under these reaction conditions (Table 5, Entry 7). Substrates **4i**–**4k** with 2-thienyl, 1-naphthyl or biphenyl groups were also tolerated for this reaction, giving high yields of products **3i**–**3k** (Table 5, Entries 8–10). The *trans*/*cis* ratios for all the fluorination products summarized in Table 5 were close to that for **3a**, and varied within a narrow range of 1.2:1 to 2.6:1, indicating little effect of the substrate structure and original *dr* value.

Table 5. Substrate scope of fluorination reaction with KHF_2.[a]



4 3

Entry	Product **3**	Time [h]	Conv. [%]	Yield [%][b]	*trans*/*cis*[c]
1	C_6H_5 **3a**	9	95	85 (81)	2.6:1
2	4-MeC_6H_4 **3b**	18	84	92 (77)	1.5:1
3	4-$MeOC_6H_4$ **3c**	18	83	86 (71)	1.2:1
4	4-ClC_6H_4 **3e**	4	96	89 (85)	1.6:1
5	4-BrC_6H_4 **3f**	4	94	81 (76)	2.2:1
6	Me **3g**	24	15	trace	–
7	MeO **3h**	24	0	–	–
8	2-thienyl **3i**	5	86	93 (80)	1.9:1
9	1-naphthyl **3j**	15	84	92 (77)	1.8:1
10	4-PhC_6H_4 **3k**	11	85	93 (79)	2.4:1

[a] Reactions were carried out with **4** (0.5 mmol), KHF_2 (3 equiv.) in DMSO (2 mL) at 120 °C for the times given. [b] Yields based on converted **4**, isolated yields in parentheses. [c] Determined by ^1H NMR spectroscopy of the crude product.

Conclusions

In summary, we have developed a convenient method for preparing valuable ethyl α-fluorocyclopropanecarboxylates that involves a convenient MIRC reaction between ethyl dichloroacetate and various terminal electron-deficient alkenes and subsequent fluorination reaction with potassium bifluoride through a 1,2-elimination/addition pathway. This methodology is very practical owing to the quite-mild reaction conditions and cheap reagents used. In addition, electron-deficient reactive cyclopropene intermediate **6**, generated in situ through a common 1,2-elimination, proved synthetically useful for accessing bicycloadducts, which are currently being investigated in our laboratory.

Experimental Section

General: Reactions were monitored by TLC analysis by using silica-gel 60 Å F-254 thin-layer plates. Flash column chromatography was performed on silica gel 60 Å, 10–40 μm. ^1H NMR spectra were recorded on a Bruker instrument (400 MHz). Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard. Data are reported as multiplicity (s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet). ^{13}C NMR spectra were recorded with a Bruker instrument (101 MHz) with complete proton decoupling. Chemical shifts are reported in ppm from the tetramethylsilane with the solvent resonance as internal standard. ^{19}F NMR spectra were recorded with a Bruker instrument (376 MHz) with $CDCl_3$ as the solvent. IR spectra were recorded with a Bruker FT-IR spectrometer. Melting points were recorded with a melting point detector. HRMS data were measured with a Waters Micromass GCT Premier with an EI source and an Apex III (7.0 Tesla) FTMS (Bruker, Billerica, MA, USA) equipped with an ESI source.

Typical Procedure for Synthesis of Monochlorinated Cyclopropane 4: Terminal electron-deficient alkene **2a** (0.5 mmol) was added to a solution of **1b** (0.5 mmol) and Cs_2CO_3 (0.6 mmol) in DMF (2 mL), and the mixture was stirred at room temperature. The reaction was followed by thin-layer chromatography until substrate **2a** disappeared. The mixture was then washed with water and extracted with CH_2Cl_2. Combined extracts were dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography to afford 90 mg of compound **4a** in 71% yield. Unless otherwise specified, all other products **4** were synthesized according to this typical procedure.

4a: Colorless oil (90 mg, 71% yield). ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.99 (m, 2 H, ArH), 7.62 (m, 1 H, ArH), 7.50 (m, 2 H, ArH), 4.34 (q, J = 7.1 Hz, 2 H, COOEt), 3.53 (dd, J = 9.1, 7.9 Hz, 1 H, CH-cyclo), 2.23 (dd, J = 7.9, 5.6 Hz, 1 H, CH_2-cyclo), 1.98 (dd, J = 9.1, 5.6 Hz, 1 H, CH_2-cyclo), 1.36 (t, J = 7.1 Hz, 3 H, COOEt) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C, TMS): δ = 191.6, 168.7, 136.9, 133.7, 128.8, 128.5, 63.2, 43.7, 33.5, 21.9, 14.1 ppm. IR (neat): $\tilde{\nu}$ = 3088, 2983, 2937, 1732, 1685, 1593, 1450, 1380, 1367, 1276, 1223, 1178, 1133, 1090, 1056, 1009, 979 cm^{-1}. HRMS (EI): calcd. for $C_{13}H_{13}ClO_3$ $[M]^+$ 252.0553; found 252.0559.

4b: White solid (93 mg, 70% yield); m.p. 27–28 °C. ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.87 (d, J = 8.2 Hz, 2 H, ArH), 7.28 (d, J = 8.0 Hz, 2 H, ArH), 4.32 (q, J = 7.1 Hz, 2 H, COOEt), 3.51 (dd, J = 9.1, 8.0 Hz, 1 H, CH-cyclo), 2.41 (s, 3 H, CH_3), 2.21 (dd, J = 7.9, 5.6 Hz, 1 H, CH_2-cyclo), 1.96 (dd, J = 9.1, 5.6 Hz, 1 H, CH_2-cyclo), 1.35 (t, J = 7.1 Hz, 3 H, COOEt) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C, TMS): δ = 191.1, 168.9, 144.7, 134.6, 129.5, 128.6, 63.2, 43.5, 33.5, 21.9, 21.7, 14.1 ppm. IR (neat): $\tilde{\nu}$ = 3100, 3032, 2983, 2936, 2873, 1740, 1727, 1682, 1607, 1448, 1407, 1379, 1367, 1276, 1229, 1210, 1180, 1134, 1087, 1058, 1012, 919 cm^{-1}. HRMS (EI): calcd. for $C_{14}H_{15}ClO_3$ $[M]^+$ 266.0710; found 266.0712.

4c: Colorless oil (107 mg, 76% yield). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.95 (d, J = 8.9 Hz, 2 H, ArH), 6.95 (d, J = 8.9 Hz, 2 H, ArH), 4.31 (q, J = 7.1 Hz, 2 H, COOEt), 3.86 (s, 3 H, OCH_3), 3.47 (dd, J = 9.1, 8.0 Hz, 1 H, CH-cyclo), 2.19 (dd, J = 8.0, 5.6 Hz, 1 H, CH_2-cyclo), 1.94 (dd, J = 9.1, 5.6 Hz, 1 H, CH_2-cyclo), 1.37 (t, J = 7.1 Hz, 3 H, COOEt) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C, TMS): δ = 189.8, 168.9, 164.0, 130.9, 130.1, 113.9, 63.2, 55.5, 43.5, 33.3, 21.9, 14.1 ppm. IR (neat): $\tilde{\nu}$ = 3101, 3074, 2981, 2938, 2841, 1735, 1675, 1597, 1511, 1461, 1421, 1379, 1367, 1309, 1266, 1170, 1133, 1086, 1057, 1023, 979, 920, 903 cm^{-1}. HRMS (EI): calcd. for $C_{14}H_{15}ClO_4$ $[M]^+$ 282.0659; found 282.0661.

4d: Colorless oil (90 mg, 60% yield). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.89 (d, J = 8.6 Hz, 2 H, ArH), 7.29 (d, J = 8.6 Hz, 2 H, ArH), 4.33 (q, J = 7.1 Hz, 2 H, COOEt), 3.49 (dd, J = 9.1, 8.0 Hz, 1 H, CH-cyclo), 2.52 (s, 3 H, SCH_3), 2.22 (dd, J = 8.0, 5.6 Hz, 1 H, CH_2-cyclo), 1.98 (dd, J = 9.1, 5.6 Hz, 1 H, CH_2-cyclo), 1.38 (t, J = 7.1 Hz, 3 H, COOEt) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C, TMS): δ = 190.4, 168.8, 146.9, 133.3, 128.9, 125.0, 63.2, 43.5, 33.4, 21.9, 14.7, 14.1 ppm. IR (neat): $\tilde{\nu}$ = 3099, 2983, 2924, 2871, 1736, 1676, 1587, 1436, 1402, 1377, 1366, 1276, 1236, 1185, 1134, 1094, 1058, 1006, 975, 920 cm^{-1}. HRMS (EI): calcd. for $C_{14}H_{15}ClO_3S$ $[M]^+$ 298.0430; found 298.0435.

4e: Colorless oil (83 mg, 58% yield). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.91 (d, J = 8.6 Hz, 2 H, ArH), 7.46 (d, J = 8.6 Hz, 2 H, ArH), 4.33 (q, J = 7.1 Hz, 2 H, COOEt), 3.48 (dd, J = 9.1, 7.9 Hz, 1 H, CH-cyclo), 2.22 (dd, J = 7.9, 5.7 Hz, 1 H, CH_2-cyclo), 1.99 (dd, J = 9.1, 5.7 Hz, 1 H, CH_2-cyclo), 1.38 (t, J = 7.1 Hz, 3 H, COOEt) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C, TMS): δ = 190.5, 168.7, 140.3, 135.3, 129.9, 129.2, 63.3, 43.6, 33.4, 22.1, 14.1 ppm. IR (neat): $\tilde{\nu}$ = 3100, 3060, 2982, 2933, 1734, 1686, 1587, 1468, 1451, 1400, 1378, 1368, 1276, 1220, 1175, 1134, 1092, 1008, 978, 919, 902, 843 cm^{-1}. HRMS (EI): calcd. for $C_{13}H_{12}Cl_2O_3$ $[M]^+$ 286.0163; found 286.0165.

4f: Colorless oil (101 mg, 61% yield). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.85 (d, J = 8.6 Hz, 2 H, ArH), 7.65 (d, J = 8.6 Hz, 2 H, ArH), 4.35 (q, J = 7.1 Hz, 2 H, COOEt), 3.49 (dd, J = 9.0, 7.9 Hz, 1 H, CH-cyclo), 2.23 (dd, J = 7.9, 5.7 Hz, 1 H, CH_2-cyclo), 2.00 (dd, J = 9.0, 5.7 Hz, 1 H, CH_2-cyclo), 1.38 (t, J = 7.1 Hz, 3 H, COOEt) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C, TMS): δ = 190.7, 168.6, 135.7, 132.2, 130.0, 129.0, 63.3, 43.6, 33.4, 22.1, 14.1 ppm. IR (neat): $\tilde{\nu}$ = 3099, 3057, 2983, 2906, 2873, 1743, 1723, 1686, 1585, 1476, 1446, 1398, 1378, 1367, 1277, 1218, 1176, 1134, 1111, 1070, 1006, 978, 919, 902, 840 cm^{-1}. HRMS (EI): calcd. for $C_{13}H_{12}BrClO_3$ $[M]^+$ 329.9658; found 329.9654.

4g: Colorless oil (72 mg, 76% yield). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 4.26 (q, J = 7.1 Hz, 2 H, COOEt), 2.91 (dd, J = 9.0, 7.9 Hz, 1 H, CH-cyclo), 2.34 (s, 3 H, CH_3), 1.96 (dd, J = 7.9, 5.7 Hz, 1 H, CH_2-cyclo), 1.84 (dd, J = 9.0, 5.7 Hz, 1 H, CH_2-cyclo), 1.32 (t, J = 7.1 Hz, 3 H, COOEt) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C, TMS): δ = 199.4, 168.6, 63.1, 43.1, 36.5, 31.6, 22.3, 14.0 ppm. IR (neat): $\tilde{\nu}$ = 3102, 2985, 2939, 1722, 1420, 1381, 1368, 1275, 1214, 1171, 1132, 1096, 1022, 985 cm^{-1}. HRMS (ESI): calcd. for $C_8H_{11}ClNaO_3$ $[M + Na]^+$ 213.02889; found 213.02896.

4h: Colorless oil (77 mg, 74% yield). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 4.22 (q, J = 7.1 Hz, 2 H, COOEt), 3.75 (s, 3 H, COOMe), 2.66 (t, J = 8.6 Hz, 1 H, CH-cyclo), 1.95 (m, 2 H, CH_2-cyclo), 1.32 (t, J = 7.1 Hz, 3 H, COOEt) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C, TMS): δ = 168.3, 167.5, 63.1, 52.6, 42.5, 30.6, 22.9, 14.0 ppm. IR (neat): $\tilde{\nu}$ = 3107, 3056, 2986, 2955, 2910, 2853, 1743, 1442, 1383, 1369, 1278, 1233, 1198, 1175, 1134, 1095, 1064, 1029, 983 cm^{-1}.

4i: Colorless oil (80 mg, 62% yield). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.79 (dd, J = 3.9, 0.9 Hz, 1 H, ArH), 7.72 (dd, J = 4.9, 0.9 Hz, 1 H, ArH), 7.18 (dd, J = 4.9, 3.9 Hz, 1 H, ArH), 4.32 (m, 2 H, COOEt), 3.49 (dd, J = 9.1, 7.9 Hz, 1 H, CH-cyclo), 2.21 (dd, J = 7.9, 5.7 Hz, 1 H, CH_2-cyclo), 2.01 (dd, J = 9.1, 5.7 Hz, 1 H, CH_2-cyclo), 1.37 (t, J = 7.1 Hz, 3 H, COOEt) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C, TMS): δ = 183.9, 168.7, 144.2, 134.7, 133.0, 128.4, 63.2, 43.8, 34.0, 22.2, 14.1 ppm. IR (neat): $\tilde{\nu}$ = 3102, 2981, 2964, 2906, 2873, 1741, 1724, 1663, 1516, 1466, 1445, 1414, 1381, 1367, 1279, 1239, 1215, 1132, 1087, 1065, 1020, 991 cm^{-1}. HRMS (EI): calcd. for $C_{11}H_{11}ClO_3S$ $[M]^+$ 258.0117; found 258.0115.

4j: Yellow oil (121 mg, 80% yield). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 8.74 (d, J = 8.7 Hz, 1 H, ArH), 7.99 (m, 3 H, ArH), 7.61 (m, 3 H, ArH), 4.36 (q, J = 7.1 Hz, 2 H, COOEt), 3.55 (dd, J = 9.0, 7.9 Hz, 1 H, CH-cyclo), 2.38 (dd, J = 7.9, 5.6 Hz, 1 H, CH_2-cyclo), 2.09 (dd, J = 9.0, 5.6 Hz, 1 H, CH_2-cyclo), 1.39 (t, J = 7.1 Hz, 3 H, COOEt) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C, TMS): δ = 194.2, 168.7, 135.4, 133.9, 133.6, 130.3, 129.1, 128.5, 128.3, 126.7, 125.7, 124.5, 63.2, 44.7, 36.5, 22.5, 14.2 ppm. IR (neat): $\tilde{\nu}$ = 3095, 3050, 2983, 2937, 2906, 1736, 1680, 1584, 1509, 1460, 1395, 1364, 1270, 1229, 1178, 1134, 1099, 1056, 1020, 977 cm^{-1}. HRMS (EI): calcd. for $C_{17}H_{15}ClO_3$ $[M]^+$ 302.0710; found 302.0709.

4k: White solid (118 mg, 72% yield); m.p. 28–29 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 8.09 (m, 2 H, ArH), 7.74 (m, 2 H, ArH), 7.66 (m, 2 H, ArH), 7.46 (m, 3 H, ArH), 4.38 (q, J = 7.1 Hz, 2 H, COOEt), 3.61 (dd, J = 9.1, 8.0 Hz, 1 H, CH-cyclo), 2.29 (dd, J = 8.0, 5.6 Hz, 1 H, CH_2-cyclo), 2.04 (dd, J = 9.1, 5.6 Hz, 1 H, CH_2-cyclo), 1.41 (t, J = 7.1 Hz, 3 H, COOEt) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C, TMS): δ = 191.1, 168.8, 146.4, 139.7, 135.7, 129.1, 129.0, 128.4, 127.5, 127.3, 63.3, 43.7, 33.6, 22.1, 14.2 ppm. IR (film): $\tilde{\nu}$ = 3057, 3032, 2983, 2937, 1733, 1681, 1602, 1449, 1405, 1377, 1276, 1228, 1192, 1133, 1083, 1058, 1027, 1006, 978 cm^{-1}. HRMS (EI): calcd. for $C_{19}H_{17}ClO_3$ $[M]^+$ 328.0866; found 328.0863.

Typical Procedure for Synthesis of Monofluorinated Cyclopropanes 3: Fluorination with KHF_2: KHF_2 (1.5 mmol) was added to a solution of **4a** (0.5 mmol) in DMSO (2 mL), and the mixture was heated and stirred at 120 °C. The reaction was followed by TLC until substrate **4a** was almost exhausted (ultraviolet absorption of **4a** was almost invisible by TLC analysis). The mixture was then washed with water and extracted with CH_2Cl_2. Combined extracts were dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography to afford 95 mg of compound **3a** in 85% yield. Unless otherwise specified, all products **3** were synthesized according to this typical procedure.

Fluorination with KF: KF (1.0 mmol) was added to a solution of **4a** (0.5 mmol) and TBAB (20 mol-%) in DMSO (2 mL), and the mixture was heated and stirred at 120 °C. The reaction was worked-up according to the above procedures. Compound **3a** was afforded in 68% yield, 80 mg.

3a: Yellowish oil (total 95 mg, 81% yield). IR (neat): $\tilde{\nu}$ = 3104, 3063, 2983, 2984, 2936, 2874, 1746, 1684, 1597, 1536, 1449, 1369, 1302, 1274, 1220, 1178, 1157, 1096, 1043, 1019, 994 cm^{-1}. HRMS (EI): calcd. for $C_{13}H_{13}FO_3$ $[M]^+$ 236.0849; found 236.0845.

Major Isomer: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 8.00 (m, 2 H, ArH), 7.58 (m, 1 H, ArH), 7.49 (m, 2 H, ArH), 4.37 (q, J = 7.1 Hz, 2 H, COOEt), 3.46 (ddd, J = 9.9, 8.2, 3.0 Hz, 1 H, CH-cyclo), 2.46 (ddd, J = 18.5, 8.2, 6.3 Hz, 1 H, CH_2-cyclo), 1.82 (m,

1 H, CH_2-cyclo), 1.37 (t, J = 7.1 Hz, 3 H, COOEt) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C, TMS): δ = 190.5, 168.5 (d, J = 24 Hz), 137.2, 133.6, 128.8, 128.4, 77.6 (d, J = 243 Hz), 62.6, 31.2 (d, J = 11 Hz), 17.7 (d, J = 17 Hz), 14.2 ppm. ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C, TMS): δ = –205.96 (ddd, J = 18.6, 8.9, 2.7 Hz) ppm.

Minor Isomer: ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 8.00 (m, 2 H, ArH), 7.58 (m, 1 H, ArH), 7.49 (m, 2 H, ArH), 4.02 (q, J = 7.1 Hz, 2 H, COOEt), 3.18 (ddd, J = 19.4, 10.8, 9.3 Hz, 1 H, CH-cyclo), 2.22 (td, J = 9.5, 6.9 Hz, 1 H, CH_2-cyclo), 1.85 (m, 1 H, CH_2-cyclo), 1.00 (t, J = 7.1 Hz, 3 H, COOEt) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C, TMS): δ = 190.8, 166.6 (d, J = 18 Hz), 136.2, 133.7, 128.8, 77.5 (d, J = 236 Hz), 62.0, 33.3 (d, J = 9 Hz), 17.1 (d, J = 10 Hz), 13.8 ppm. ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C, TMS): δ = –183.43 (ddd, J = 18.7, 17.0, 9.6 Hz) ppm.

3b: Yellowish oil (total 97 mg, 77% yield). IR (neat): $\tilde{\nu}$ = 3104, 2984, 2928, 2872, 1747, 1683, 1607, 1447, 1403, 1373, 1335, 1301, 1262, 1225, 1211, 1179, 1157, 1116, 1097, 1043, 1018, 934 cm^{-1}. HRMS (EI): calcd. for $C_{14}H_{15}FO_3$ $[M]^+$ 250.1005; found 250.1007.

Major Isomer: ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.91 (m, 2 H, ArH), 7.29 (m, 2 H, ArH), 4.37 (q, J = 7.1 Hz, 2 H, COOEt), 3.44 (ddd, J = 9.4, 8.3, 3.0 Hz, 1 H, CH-cyclo), 2.45 (m, 1 H, CH_2-cyclo), 2.43 (s, 3 H, CH_3), 1.81 (m, 1 H, CH_2-cyclo), 1.38 (t, J = 7.1 Hz, 3 H, COOEt) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C, TMS): δ = 190.0, 168.6 (d, J = 24 Hz), 144.6, 134.8, 129.5, 128.5, 77.5 (d, J = 243 Hz), 62.5, 31.2 (d, J = 11 Hz), 21.7, 17.7 (d, J = 11 Hz), 14.2 ppm. ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C, TMS): δ = –206.13 (ddd, J = 18.2, 8.9, 2.7 Hz) ppm.

Minor Isomer: ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.91 (m, 2 H, ArH), 7.29 (m, 2 H, ArH), 4.02 (q, J = 7.1 Hz, 2 H, COOEt), 3.16 (ddd, J = 19.9, 10.8, 9.4 Hz, 1 H, CH-cyclo), 2.42 (s, 3 H, CH_3), 2.21 (td, J = 9.5, 6.9 Hz, 1 H, CH_2-cyclo), 1.81 (m, 1 H, CH_2-cyclo), 1.01 (t, J = 7.1 Hz, 3 H, COOEt) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C, TMS): δ = 190.4, 166.7 (d, J = 25 Hz), 144.6, 133.8, 129.5, 128.5, 77.4 (d, J = 235 Hz), 62.0, 33.3 (d, J = 9 Hz), 21.7, 17.0 (d, J = 10 Hz), 13.8 ppm. ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C, TMS): δ = –183.45 (ddd, J = 19.1, 17.4, 9.8 Hz) ppm.

3c: Yellowish oil (total 95 mg, 71% yield). IR (neat): $\tilde{\nu}$ = 3105, 3052, 2982, 2938, 2912, 2843, 1745, 1675, 1601, 1578, 1511, 1464, 1423, 1380, 1368, 1304, 1262, 1229, 1174, 1114, 1024, 993, 932, 849 cm^{-1}. HRMS (EI): calcd. for $C_{14}H_{15}FO_4$ $[M]^+$ 266.0954; found 266.0952.

Major Isomer: ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.98 (d, J = 8.9 Hz, 2 H, ArH), 6.97 (d, J = 8.9 Hz, 2 H, ArH), 4.37 (q, J = 7.1 Hz, 2 H, COOEt), 3.88 (s, 3 H, OCH_3), 3.41 (ddd, J = 9.5, 8.2, 3.1 Hz, 1 H, CH-cyclo), 2.44 (ddd, J = 18.5, 8.2, 6.2 Hz, 1 H, CH_2-cyclo), 1.79 (m, 1 H, CH_2-cyclo), 1.38 (t, J = 7.1 Hz, 3 H, COOEt) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C, TMS): δ = 188.7, 168.7 (d, J = 24 Hz), 130.7, 130.3, 113.9, 77.4 (d, J = 242 Hz), 62.5, 55.5, 31.0 (d, J = 11 Hz), 17.6 (d, J = 10 Hz), 14.2 ppm. ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C, TMS): δ = –206.22 (m) ppm.

Minor Isomer: ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.99 (m, 2 H, ArH), 6.97 (m, 2 H, ArH), 4.02 (m, 2 H, COOEt), 3.88 (s, 3 H, OCH_3), 3.13 (ddd, J = 19.8, 10.9, 9.3 Hz, 1 H, CH-cyclo), 2.20 (td, J = 9.5, 6.9 Hz, 1 H, CH_2-cyclo), 1.81 (m, 1 H, CH_2-cyclo), 1.01 (t, J = 7.1 Hz, 3 H, COOEt) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C, TMS): δ = 189.3, 163.9 (d, J = 18 Hz), 130.7, 129.4, 114.0, 77.4 (d, J = 235 Hz), 61.9, 55.5, 33.2 (d, J = 10 Hz), 17.0 (d, J = 10 Hz), 13.8 ppm. ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C, TMS): δ = –183.65 (ddd, J = 18.7, 17.1, 9.6 Hz) ppm.

3e: Colorless oil (total 116 mg, 85% yield). IR (neat): $\tilde{\nu}$ = 3103, 3065, 2985, 2937, 2874, 1745, 1686, 1590, 1484, 1469, 1445, 1401, 1378, 1335, 1307, 1275, 1218, 1178, 1157, 1093, 1041, 1014, 993, 932, 851 cm^{-1}. HRMS (EI): calcd. for $C_{13}H_{12}ClFO_3$ $[M]^+$ 270.0459; found 270.0456.

Major Isomer: ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.92 (d, J = 8.6 Hz, 2 H, ArH), 7.46 (d, J = 8.6 Hz, 2 H, ArH), 4.36 (q, J = 7.1 Hz, 2 H, COOEt), 3.40 (ddd, J = 9.4, 8.3, 2.9 Hz, 1 H, CH-cyclo), 2.45 (ddd, J = 18.5, 8.1, 6.4 Hz, 1 H, CH_2-cyclo), 1.84 (m, 1 H, CH_2-cyclo), 1.37 (t, J = 7.1 Hz, 3 H, COOEt) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C, TMS): δ = 189.3, 168.3 (d, J = 24 Hz), 140.1, 135.5, 129.8, 129.1, 77.6 (d, J = 244 Hz), 62.7, 31.1 (d, J = 11 Hz) 17.8 (d, J = 10 Hz), 14.1 ppm. ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C, TMS): δ = –205.75 (ddd, J = 18.6, 9.8, 2.6 Hz) ppm.

Minor Isomer: ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.95 (d, J = 8.6 Hz, 2 H, ArH), 7.46 (d, J = 8.6 Hz, 2 H, ArH), 4.04 (q, J = 7.1 Hz, 2 H, COOEt), 3.13 (ddd, J = 19.1, 10.7, 9.4 Hz, 1 H, CH-cyclo), 2.21 (td, J = 9.5, 7.0 Hz, 1 H, CH_2-cyclo), 1.86 (m, 1 H, CH_2-cyclo), 1.03 (t, J = 7.1 Hz, 3 H, COOEt) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C, TMS): δ = 189.7, 166.7 (d, J = 25 Hz), 140.2, 134.6, 129.7, 129.2, 77.4 (d, J = 237 Hz), 62.1, 33.1 (d, J = 10 Hz), 17.1 (d, J = 9 Hz), 13.8 ppm. ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C, TMS): δ = –183.41 (m) ppm.

3f: Yellowish oil (total 120 mg, 76% yield). IR (neat): $\tilde{\nu}$ = 3101, 3066, 2958, 2922, 2869, 2851, 1742, 1685, 1585, 1465, 1398, 1378, 1308, 1272, 1217, 1178, 1156, 1095, 1069, 1010, 932, 847, 777 cm^{-1}. HRMS (EI): calcd. for $C_{13}H_{12}BrFO_3$ $[M]^+$ 313.9954; found 313.9958.

Major Isomer: ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.84 (d, J = 8.6 Hz, 2 H, ArH), 7.63 (d, J = 8.6 Hz, 2 H, ArH), 4.36 (q, J = 7.1 Hz, 2 H, COOEt), 3.39 (ddd, J = 9.4, 8.2, 2.9 Hz, 1 H, CH-cyclo), 2.44 (ddd, J = 18.5, 8.1, 6.4 Hz, 1 H, CH_2-cyclo), 1.84 (m, 1 H, CH_2-cyclo), 1.37 (t, J = 7.1 Hz, 3 H, COOEt) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C, TMS): δ = 189.5, 168.3 (d, J = 24 Hz), 135.9, 132.1, 129.9, 128.9, 77.6 (d, J = 244 Hz), 62.7, 31.1 (d, J = 11 Hz), 17.9 (d, J = 11 Hz), 14.2 ppm. ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C, TMS): δ = –205.70 (ddd, J = 18.6, 9.8, 2.6 Hz) ppm.

Minor Isomer: ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.87 (d, J = 8.6 Hz, 2 H, ArH), 7.63 (d, J = 8.6 Hz, 2 H, ArH), 4.04 (q, J = 7.1 Hz, 2 H, COOEt), 3.13 (ddd, J = 19.1, 10.7, 9.3 Hz, 1 H, CH-cyclo), 2.21 (td, J = 9.5, 7.0 Hz, 1 H, CH_2-cyclo), 1.84 (m, 1 H, CH_2-cyclo), 1.03 (t, J = 7.1 Hz, 3 H, COOEt) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C, TMS): δ = 189.9, 166.5 (d, J = 25 Hz), 135.0, 132.2, 129.8, 129.0, 77.4 (d, J = 237 Hz), 62.1, 33.1 (d, J = 10 Hz), 17.1 (d, J = 9 Hz), 13.8 ppm. ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C, TMS): δ = –183.37 (m) ppm.

3i: Yellowish oil (total 97 mg, 80% yield). IR (neat): $\tilde{\nu}$ = 3104, 2976, 2928, 1745, 1664, 1516, 1466, 1446, 1413, 1371, 1335, 1307, 1240, 1157, 1085, 1064, 1050, 1016, 982, 915, 854, 731 cm^{-1}. HRMS (EI): calcd. for $C_{11}H_{11}FO_3S$ $[M]^+$ 242.0413; found 242.0415.

Major Isomer: ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.81 (m, 1 H, ArH), 7.70 (m, 1 H, ArH), 7.16 (m, 1 H, ArH), 4.35 (q, J = 7.1 Hz, 2 H, COOEt), 3.35 (ddd, J = 9.6, 8.2, 2.7 Hz, 1 H, CH-cyclo), 2.43 (ddd, J = 18.5, 8.0, 6.4 Hz, 1 H, CH_2-cyclo), 1.83 (m, 1 H, CH_2-cyclo), 1.36 (t, J = 7.1 Hz, 3 H, COOEt) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C, TMS): δ = 182.9, 168.4 (d, J = 24 Hz), 144.5, 134.6, 132.7, 128.4, 77.5 (d, J = 245 Hz), 62.6, 31.7 (d, J =

11 Hz), 17.9 (d, J = 11 Hz), 14.1 ppm. ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C, TMS): δ = –205.87 (ddd, J = 18.8, 8.9, 2.3 Hz) ppm.

Minor Isomer: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.81 (m, 1 H, ArH), 7.70 (m, 1 H, ArH), 7.16 (m, 1 H, ArH), 4.08 (m, 2 H, COOEt), 3.16 (ddd, J = 19.0, 10.8, 9.3 Hz, 1 H, CH-cyclo), 2.22 (td, J = 9.5, 7.0 Hz, 1 H, CH_2-cyclo), 1.83 (m, 1 H, CH_2-cyclo), 1.06 (t, J = 7.1 Hz, 3 H, COOEt) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C, TMS): δ = 183.6, 166.5 (d, J = 25 Hz), 143.5, 134.5, 132.9, 128.4, 77.5 (d, J = 235 Hz), 62.1, 33.5 (d, J = 11 Hz), 17.2 (d, J = 10 Hz), 13.8 ppm. ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C, TMS): δ = –183.16 (m) ppm.

3j: Yellowish oil (total 111 mg, 77% yield). IR (neat): $\tilde{\nu}$ = 3057, 2958, 2921, 2851, 1743, 1680, 1592, 1574, 1508, 1462, 1399, 1376, 1333, 1301, 1274, 1230, 1177, 1157, 1101, 1018, 920, 864, 785, 764, 749 cm^{-1}. HRMS (EI): calcd. for $C_{17}H_{15}FO_3$ $[M]^+$ 286.1005; found 286.1001.

Major Isomer: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 8.64 (d, J = 8.7 Hz, 1 H, ArH), 8.03 (d, J = 8.4 Hz, 1 H, ArH), 7.96 (dd, J = 7.2, 1.1 Hz, 1 H, ArH), 7.90 (dd, J = 7.7, 1.2 Hz, 1 H, ArH), 7.63 (m, 1 H, ArH), 7.56 (m, 2 H, ArH), 4.38 (q, J = 7.1 Hz, 2 H, COOEt), 3.43 (ddd, J = 9.4, 8.2, 2.8 Hz, 1 H, CH-cyclo), 2.61 (ddd, J = 18.4, 8.1, 6.3 Hz, 1 H, CH_2-cyclo), 1.92 (m, 1 H, CH_2-cyclo), 1.39 (t, J = 7.1 Hz, 3 H, COOEt) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C, TMS): δ = 193.5, 168.3 (d, J = 24 Hz), 135.9, 133.9, 133.3, 130.5, 130.1, 128.5, 128.2, 126.7, 125.6, 124.5, 78.2 (d, J = 201 Hz), 62.6, 34.6 (d, J = 11 Hz), 18.2 (d, J = 10 Hz), 14.2 ppm. ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C, TMS): δ = –205.34 (m) ppm.

Minor Isomer: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 8.96 (d, J = 8.0 Hz, 1 H, ArH), 8.19 (dd, J = 7.3, 1.1 Hz, 1 H, ArH), 8.05 (d, J = 8.7 Hz, 1 H, ArH), 7.96 (dd, J = 7.2, 1.1 Hz, 1 H, ArH), 7.64 (ddd, J = 8.6, 3.5, 1.6 Hz, 1 H, ArH), 7.56 (m, 2 H, ArH), 4.06 (tdd, J = 10.8, 7.1, 3.6 Hz, 2 H, COOEt), 3.32 (ddd, J = 19.8, 10.8, 9.3 Hz, 1 H, CH-cyclo), 2.36 (ddd, J = 9.9, 9.3, 6.9 Hz, 1 H, CH_2-cyclo), 1.92 (m, 1 H, CH_2-cyclo), 1.03 (t, J = 7.1 Hz, 3 H, COOEt) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C, TMS): δ = 193.3, 166.7 (d, J = 25 Hz), 134.2, 134.0, 133.4, 130.4, 130.1, 128.5, 128.4, 126.7, 126.0, 124.4, 78.3 (d, J = 258 Hz), 62.1, 35.5 (d, J = 9 Hz), 17.7 (d, J = 9 Hz), 13.9 ppm. ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C, TMS): δ = –182.16 (ddd, J = 19.3, 17.5, 10.0 Hz) ppm.

3k: Yellow solid (total 123 mg, 79% yield); m.p. 30–31 °C. IR (film): $\tilde{\nu}$ = 3106, 3073, 3011, 2983, 2875, 1744, 1665, 1603, 1560, 1516, 1482, 1448, 1402, 1383, 1367, 1335, 1298, 1230, 1176, 1098, 1021, 935, 908, 858, 758, 697 cm^{-1}. HRMS (EI): calcd. for $C_{19}H_{17}FO_3$ $[M]^+$ 312.1162; found 312.1164.

Major Isomer: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 8.10 (m, 2 H, ArH), 7.74 (m, 2 H, ArH), 7.65 (m, 2 H, ArH), 7.50 (m, 2 H, ArH), 7.43 (m, 1 H, ArH), 4.41 (q, J = 7.1 Hz, 2 H, COOEt), 3.52 (ddd, J = 9.4, 8.2, 3.0 Hz, 1 H, CH-cyclo), 2.52 (ddd, J = 18.5, 8.2, 6.3 Hz, 1 H, CH_2-cyclo), 1.87 (m, 1 H, CH_2-cyclo), 1.41 (t, J = 7.1 Hz, 3 H, COOEt) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C, TMS): δ = 190.0, 168.5 (d, J = 24 Hz), 146.3, 139.7, 136.0, 129.0, 128.4, 127.4, 127.3, 77.6 (d, J = 243 Hz), 62.6, 31.3 (d, J = 11 Hz), 17.8 (d, J = 10 Hz), 14.2. ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C, TMS): δ = –205.80 (m) ppm.

Minor Isomer: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 8.10 (m, 2 H, ArH), 7.74 (m, 2 H, ArH), 7.64 (m, 2 H, ArH), 7.50 (m, 2 H, ArH), 7.43 (m, 1 H, ArH), 4.07 (m, 2 H, COOEt), 3.22 (ddd, J = 19.4, 10.8, 9.3 Hz, 1 H, CH-cyclo), 2.28 (td, J = 9.5, 6.9 Hz, 1 H, CH_2-cyclo), 1.88 (m, 1 H, CH_2-cyclo), 1.06 (t, J = 7.1 Hz, 3 H, COOEt) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C, TMS): δ = 190.4, 166.7 (d, J = 25 Hz), 146.3, 139.6, 135.0, 129.0, 128.4, 127.4, 127.3, 77.5 (d, J = 234 Hz), 62.0, 33.3 (d, J = 9 Hz), 17.1 (d, J = 9 Hz), 13.8 ppm. ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C, TMS): δ = –183.34 (ddd, J = 19.1, 17.3, 9.8 Hz) ppm.

Ethyl 1-Chloro-2-[hydroxy(phenyl)methyl]cyclopropanecarboxylate (7a): To a solution of **4a** (0.5 mmol) in CH_3OH (1 mL) was added $NaBH_4$ (0.5 mmol) slowly under an ice-water bath with continuous stirring. The reaction was followed by thin-layer chromatography and stopped when substrate **4a** disappeared. The mixture was then washed with water and extracted with CH_2Cl_2. Combined extracts were dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography to afford compound **7a** as colorless oil (127 mg, in 100% yield). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.39 (m, 5 H, ArH), 4.58 (d, J = 9.5 Hz, 1 H, CH), 4.21 (q, J = 7.1 Hz, 2 H, COOEt), 2.91 (s, 1 H, OH), 2.23 (ddd, J = 10.1, 9.6, 8.2 Hz, 1 H, CH-cyclo), 1.82 (dd, J = 10.2, 5.9 Hz, 1 H, CH_2-cyclo), 1.30 (m, 1 H, CH_2-cyclo), 1.30 (t, J = 7.1 Hz, 3 H, COOEt) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C, TMS): δ = 169.8, 141.9, 128.6, 128.1, 126.2, 74.8, 62.7, 44.3, 35.9, 23.8, 14.1 ppm. IR (neat): $\tilde{\nu}$ = 3492, 3088, 3062, 3030, 2983, 2935, 2905, 1720, 1603, 1493, 1451, 1394, 1372, 1302, 1250, 1220, 1175, 1142, 1117, 1081, 1056, 1020, 968, 916, 860, 767, 740, 701, 509 cm^{-1}. HRMS (EI): calcd. for $C_{13}H_{15}ClO_3$ $[M]^+$ 254.0710; found 254.0713.

Ethyl 2-Benzoyl-2-bromo-1-chlorocyclopropanecarboxylate (8a): To a solution of **4a** (2 mmol) in CH_3COOH (1 mL) was added dropwise a mixture of Br_2 (130 μL, 2.5 mmol) and CH_3COOH (250 μL) at 118 °C. The mixture was reacted at that temperature for 3 h. After the reaction was complete, water was added to quench the reaction. The mixture was then extracted with CH_2Cl_2 and washed with 10% aqueous Na_2CO_3. Combined extracts were dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography to afford compound **8a** as colorless oil (330 mg, in 50% yield). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.98 (m, 2 H, ArH), 7.60 (m, 1 H, ArH), 7.49 (m, 2 H, ArH), 3.82 (m, 2 H, COOEt), 2.88 (d, J = 8.3 Hz, 1 H, CH_2-cyclo), 1.91 (d, J = 8.3 Hz, 1 H, CH_2-cyclo), 0.93 (t, J = 7.1 Hz, 3 H, COOEt) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C, TMS): δ = 187.5, 165.7, 134.0, 132.6, 129.5, 128.8, 63.3, 47.7, 43.4, 29.7, 13.4 ppm. IR (film): $\tilde{\nu}$ = 3094, 3064, 2982, 2965, 2926, 1748, 1726, 1690, 1596, 1449, 1398, 1370, 1316, 1267, 1225, 1179, 1132, 1069, 1026, 943, 805, 696 cm^{-1}. HRMS (ESI): calcd. for $C_{13}H_{12}BrClNaO_3$ $[M + Na]^+$ 352.95506; found 352.95545.

Capture Experiment of Cyclopropene Intermediate 6a: To a solution of **4a** (0.3 mmol) and TBAB (20 mol-%) in DMSO (1 mL) was added KF (0.6 mmol) and anthracene (0.6 mmol), and the mixture was heated and stirred at 120 °C. The reaction was detected by thin-layer chromatography until substrate **4a** disappeared. The mixture was then washed with water and extracted with CH_2Cl_2. Combined extracts were dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography to afford 25 mg of yellowish oil **3a** and 30 mg of white solid **9a**, respectively, in 35% and 25% yield.

Compound 9a: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.84 (m, 2 H, ArH), 7.58 (m, 2 H, ArH), 7.46 (t, J = 7.7 Hz, 2 H, ArH), 7.32 (m, 2 H, ArH), 7.23 (m, 2 H, ArH), 7.11 (m, 3 H, ArH), 4.95 (s, 1 H, CH-cyclo), 4.59 (s, 1 H, CH-cyclo), 4.02 (m, 2 H, COOEt), 1.98 (d, J = 5.8 Hz, 1 H, CH_2-cyclo), 1.11 (t, J = 7.1 Hz, 3 H, COOEt), 0.95 (d, J = 5.8 Hz, 1 H, CH_2-cyclo) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C, TMS): δ = 195.2, 171.6, 144.6, 143.1, 141.3, 139.8, 135.9, 133.0, 129.2, 128.5, 126.9, 126.8, 125.9, 125.8,

125.5, 125.0, 124.7, 124.3, 61.1, 48.7, 46.4, 46.1, 37.7, 25.6, 13.9 ppm. IR (film): $\tilde{\nu}$ = 3066, 3022, 2957, 2924, 2852, 1721, 1679, 1596, 1460, 1371, 1348, 1315, 1291, 1249, 1218, 1172, 1150, 1114, 1069, 1019, 976, 887, 753 cm^{-1}. HRMS (EI): calcd. for $C_{27}H_{22}O_3$ $[M]^+$ 394.1569; found 394.1567.

Supporting Information (see footnote on the first page of this article): Detailed information for the optimization of the fluorination reaction; copies of ^1H, ^{13}C, ^{19}F, HSQC and HMBC NMR spectra for all compounds; X-ray structure of **4b**.

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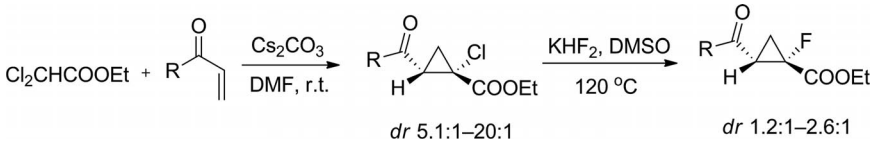

A convenient two-step method to prepare ethyl α-fluorocyclopropanecarboxylates has been developed. Ethyl α-chlorocyclopropanecarboxylates were obtained through Michael-initiated ring closure reactions under mild reaction conditions in good yields before being smoothly converted into the corresponding monofluorinated analogues through halogen exchange reactions with potassium bifluoride in good yields. The reaction mechanism was also investigated.

Keywords: Synthetic methods / Fluorine / Small-ring systems / Elimination / Nucleophilic addition

