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A stereoselective preparation of 1-fluorocyclopropane-1-carboxylate derivatives through radical addition of fluoroiodoacetate to alkenes followed by intramolecular substitution reaction

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Abstract—Triethylborane mediated iodine atom-transfer radical addition of fluoroiodoacetate to 1-alkene or cyclic alkene proceeded in a good yield to give the α-fluoro-γ-iodo esters in non-diastereoselective manner, while the subsequent cyclopropane formation via enolate of the α-fluoro ester provided the corresponding fluorocyclopropanecarboxylate in a highly *cis*- or F-*endo*-selective manner. © 2001 Elsevier Science Ltd. All rights reserved.

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1. Introduction

Organofluorine compounds are widely applied in bio- and medicinal chemistry due to their unique properties.[1] The usefulness of the fluorinated cyclopropane moiety has been demonstrated in modification of biologically active substances, in which the conformational restriction and the alteration of chemical and physical properties of functional groups are brought about by this unit.[2–4] For the synthesis of the fluorinated cyclopropane derivatives, in particular 1-fluorocyclopropane-1-carboxylate derivatives, there remains several problems to be solved. For example, the mercurial carbenoid reagent PhHgCXFCOOR (X=Cl, Br) is known as only one CFCOOR transfer reagent to electron-rich alkenes to give 1-fluorocyclopropane-1-carboxylate derivatives, although high temperature and long reaction time are required, the yields of the products severely vary depending on the structure of alkenes, and the toxicity of organomercurials is also disadvantage of this reagent.[5] Simmons–Smith reaction with fluoroallyl alcohol derivatives proceeds in stereospecific manner, although large excess of the zinc reagent is required to obtain the cyclopropane in reasonable yield due to the low reactivity of fluorinated olefins, and this reaction cannot be applied to the preparation of 2,3-disubstituted 1-fluorocyclopropane derivatives including bicyclo[*n*.1.0] ring systems.[6] Intramolecular cyclopropanation reaction of metal carbenoid derived from α-diazocarbonyl with fluorinated olefin part was also reported, while there needs multiple steps for the preparation of the precursor diazocarbonyl compounds and stereoselective synthesis of fluorinated olefin part should be also required to achieve the stereoselective preparation of the corresponding cyclopropane derivative.[3,7]

For the preparation 1-fluorocyclopropane-1-carboxylate of bicyclo[*n*.1.0] ring system, we examined the conjugate addition of bromofluoroacetate with cyclic enones followed by enolate driven intramolecular cyclopropane formation (Scheme 1). Thus, the reaction of ketene triethylsilylacetal **1**,[8] prepared in situ by treating dibromofluoroacetate with triethylsilyl chloride and Zn in CH_3CN, with cyclopentenone gave the 1,4-adduct **2** in 61% yield as a diastereomeric mixture (ratio 1.5:1) accompanied by the formation of 1,2-adduct **3** (20% yield). After separation of the diastereomers by silica gel column, each isomer (**2a**, **2b**) was treated with DBU in DMF at room temperature to give the fluorocyclopropane carboxylate (*endo*-**4**, *exo*-**4**)[3] as a single isomer in good yield, respectively. In this case, it is obvious that the stereochemical outcome of this *cis*-fused fluorocyclopropane carboxylate **4** (*endo* vs *exo*) depends on the diastereoselection in the 1,4-addition step, but unfortunately it was almost non-selective with cyclopentenone and cyclohexenone.

As an alternative method for the preparation of 2-substituted or 2,3-disubstituted 1-fluorocyclopropane-1-carboxylate, we have developed two-step procedure which involves iodine atom-transfer radical addition of fluoroiodoacetate to alkene followed by intramolecular substitution reaction of the enolate of α-fluoro ester. It would be expected that

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Keywords: fluorocyclopropanes; radical reaction; triethylborane; fluoroiodoacetate.

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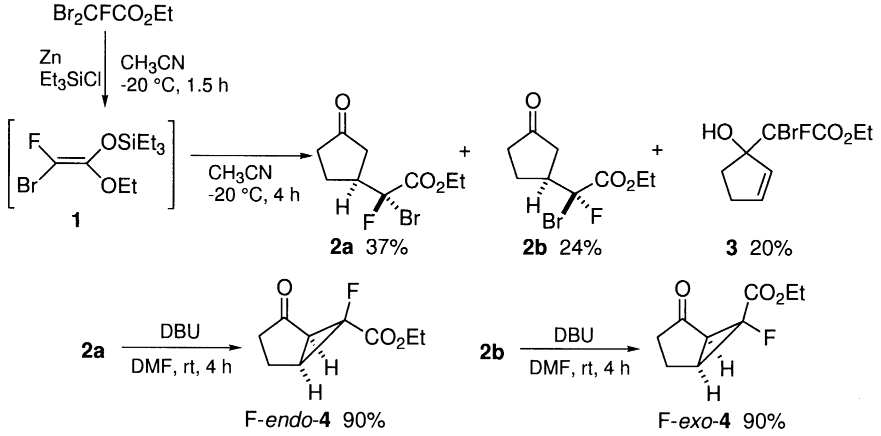
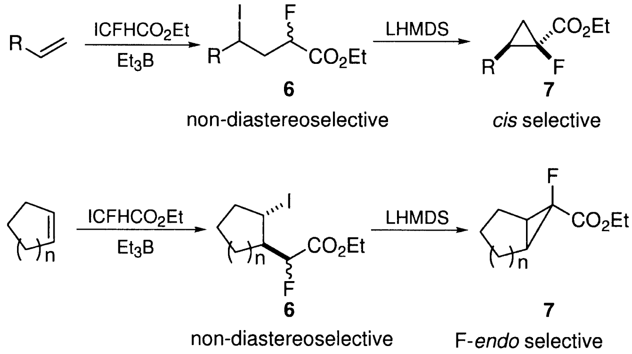


Scheme 1.



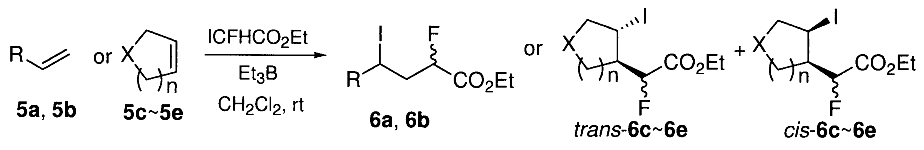
Scheme 2.

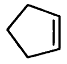
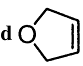
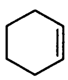
even if radical addition of fluoroiodoacetate with 1-alkene proceeds in non-diastereoselective manner, relative stereochemistry at the stereogenic center having ester group and fluorine atom can be neglected in the cyclization stage, because this position is converted to an enolate form by treating with base. Likewise, in the case of cyclic alkene, while addition of fluoroiodoacetate forms an adduct having consecutive three chiral centers, that is, which theoretically consists of four diastereomers, two *trans* isomers of these four isomers would be possibly cyclized through SN2 pathway to give the *cis*-fused bicyclo[*n*.1.0] ring system (Scheme 2). Therefore, *trans*-selectivity in the first radical addition step would be crucial for the efficiency of this method. In this paper, we report the results with particular emphasis on the stereochemical outcome in the cyclization step.

2. Results and discussion

Radical addition of fluoroiodoacetate[9] to alkenes have been reported by two groups.[10,11] Barton et al. reported that zinc and nickel dichloride hexahydrate promote this addition reaction to obtain the corresponding iodine-free α-fluoro esters.[10] Later, Chen et al. reported the iodine atom-transfer addition with electron-rich alkenes promoted by acid-washed iron powder under THF refluxing conditions to afford α-fluoro-γ-iodo esters.[11] Under the iron powder mediated conditions (THF, reflux, 10–24 h), electron-rich 1-alkenes having a variety of functional groups reacted smoothly to give the α-fluoro-γ-iodo esters in good yields, while with cyclic alkenes such as cyclohexene the yield of the adduct was not good and the stereoselectivity of this reaction was not clear (vide infra). It has been well documented that triethylborane (in the presence of oxygen) is an excellent radical initiator in the radical reaction of alkyl halides or tinhydride since the first report by Oshima et al.[12] To improve the yield of the adducts **6** as well as stereoselectivity in the cases of cyclic alkenes (*cis* vs *trans*), triethylborane mediated reaction of fluoroiodoacetate with alkenes were conducted. Results are shown in Table 1. As expected, reaction proceeded at room temperature within a relatively short time to give the iodine containing adducts **6** in good yields. With 1-alkene **5a**, **5b**, diastereoselectivities of the products was low (1.7:1 for **6a**, 1.1:1 for **6b**, respectively) (entries 1–4). Reaction with cyclic alkenes proceeded smoothly to give the *trans* isomer predominantly. For example, when the reaction was carried out at room temperature, cyclopentene gave the adduct **6c** in 69% yield with a ratio of *trans*/*cis*=5 (entry 5), 2,5-dihydrofuran gave **6d** in 43% yield with *trans*/*cis*=9.8 (entry 7) and cyclohexene gave **6e** in 69% yield with *trans*/*cis*=1.9 (entry 8). The use of Lewis acids in radical reactions with alkenes were reported to improve the reactivity of atom-transfer reactions of α-halo esters, amides, or oxazolidinone imides.[13–15] In our case, as shown in entries 6 and 9, by the addition of Lewis acid (Et$_2$AlCl) the atom transfer reaction proceeded at low temperature (−78°C) within 1 h to give **6c** (61% yield) and **6e** (69 % yield), respectively, and increase in *trans*-selectivity was observed in the case of **6c** (*trans*/*cis*=8). The role of Et$_2$AlCl should increase both the rate of addition of the electrophilic α-carbonyl radical to the alkene and also the iodine abstraction from fluoroiodoacetate by the resulting nucleophilic carbon radical due to increasing the electron-withdrawing nature of ester group by complexation with Et$_2$AlCl, thereby the reaction proceeded at low temperature. The *trans* or *cis* stereochemistries of the adduct **6c**, **6d**, **6e** were determined by NOE experiments of each isomer after separation by MPLC. The diastereomer ratio of *trans*-**6c** due to the fluorine-bearing chiral center was 1.2:1, and 1.4:1 for *cis*-**6c**. Similarly, low diastereoselectivity was observed in the case of cyclohexene (1.6:1 for *trans*-**6e**). Thus, with cyclic alkenes, atom-transfer addition of fluoroiodoacetate mediated by triethylborane proceeded in a high *trans*-selectivity with low diastereoselectivity with respect to fluorine-bearing chiral center. It should be noted that

Table 1. Atom-transfer addition of $ICFHCO_2Et$ to alkene

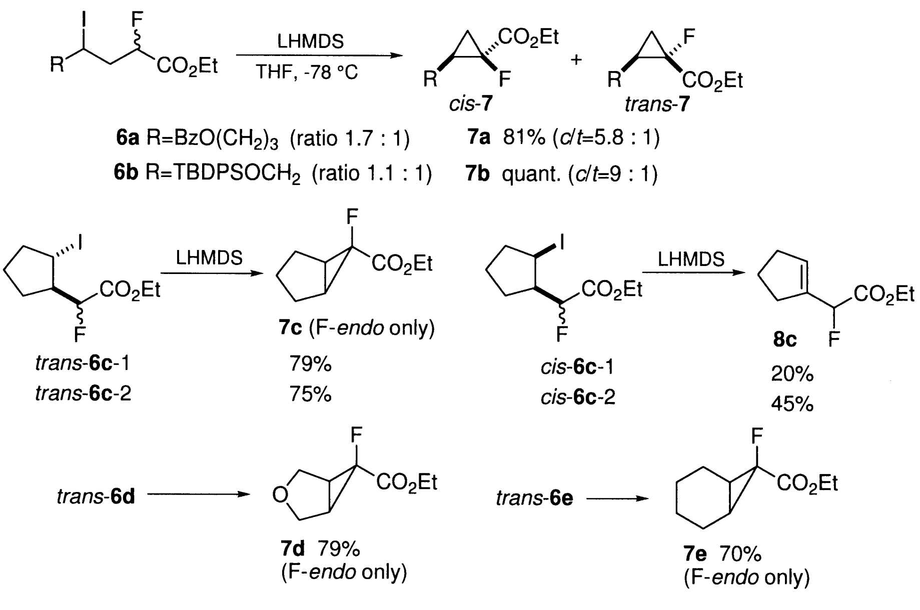


Entry	Alkene	Molar ratio[a]	Time (h)	6	Yield (%)[b]	Isomer ratio[c]
1	**5a** R=$BzO(CH_2)_3$–	1:1.5:1	7	**6a**	88	1.7:1
2[d]	**5a**	1:1.5:1	5	**6a**	73	1.8:1
3	**5b** R=$TBDPSOCH_2$–	1:1.5:1	3	**6b**	54	1.1:1
4	**5b**	1:3:1	3	**6b**	73	1.1:1
5	**5c** 	4:1:1	8	**6c**	69	*t*/*c*=5:1, *trans* 1.2:1, *cis* 1.4:1
6	**5c**	4:1:1[e]	1	**6c**	61	*t*/*c*=8:1, *trans* 1.5:1, *cis* 4.3:1
7	**5d** 	4:1:1	1	**6d**	43	*t*/*c*=9.8:1, *trans* 1.1:1, *cis* 1.2:1
8	**5e** 	4:1:1	4	**6e**	69	*t*/*c*=1.9:1, *trans* 1.7:1, *cis* 1.9:1
9	**5e**	4:1:1[e]	1	**6e**	69	*t*/*c*=1.7:1, *trans* 1.2:1, *cis* 2.2:1

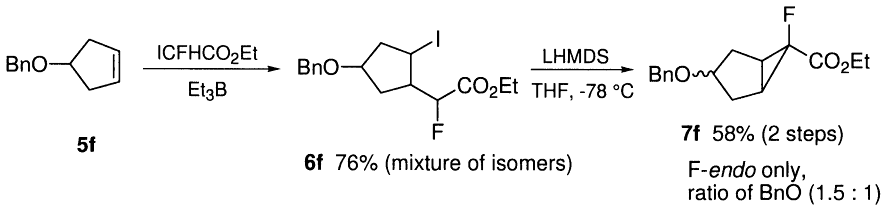
[a] Molar ratio; alkene: $ICFHCO_2Et/Et_3B$.
[b] Isolated yield.
[c] Determined by ^1H and ^{19}F NMR.
[d] Solvent; hexane.
[e] In this case, 1 equiv. of Et_2AlCl was added and reaction was carried out at −78°C.

stereochemical assignments of **6c**, **6e** reported by Chen et al.[11] are wrong. Although they reported that the *cis*/*trans* ratio of both **6c** and **6e** is almost 1:1, NMR data reported are coincide with *trans* isomers, not with *cis* isomers in comparison with our NMR data of all the isomers obtained in pure forms after MPLC purification. That is, the *cis* isomer they assigned should be another diastereomer of *trans* isomer. In fact, we re-examined the reaction of fluoroiodoactate with cyclopentene under the reported conditions (20 mol% iron powder, THF, reflux) to reveal that **6c** was obtained as a mixture of four isomers in a ratio of 2.3:2.0:1.6:1 and the former two isomers are *trans*-**6c** and the latter two isomers are *cis*-**6c**. Under the similar conditions, cyclohexene gave the adduct **6e** in a ratio of *trans*-1/*trans*-2/*cis*-1/*cis*-2=4.6:5.5:1:3.6 (To specify each diastereomer of *trans*-**6** or *cis*-**6**, compound numbers *trans*-**6**-1/*trans*-**6**-2 or *cis*-**6**-1/*cis*-**6**-2 are used on the basis of the order of elution on MPLC as indicated in Section 3).

Next, we examined the cyclopropane formation of the iodofluoro esters **6** obtained by the above reaction. It was found that LHMDS [$LiN(SiMe_3)_2$] is a suitable base for cyclopropane formation and regardless of the diastereomeric ratio of the iodofluoro esters **6** reaction proceeds in a highly



Scheme 3.



Scheme 4.

stereoselective manner to give the *cis*-2-substituted 1-fluorocyclopropane-1-carboxylate **7a**, **7b** from **6a**, **6b** and only F-*endo*-bicyclo[*n*.1.0] ring compound **7c**–**7e** from *trans*-**6c**–**6e** (see Scheme 3). For example, reaction of a diastereomeric mixture of **6a** (1.7:1) was treated with LHMDS (3.2 equiv.) in THF at −78°C for 3 h to give the cyclopropane **7a** in 81% yield (*cis*/*trans*=5.8). The use of LDA instead of LHMDS resulted in decrease in the yield of **7a** (33% yield) along with the formation of β-elimination product, 2-fluoro-7-benzoyloxy-3-heptenoate, in 18% yield. Similarly, treatment of **6b** with LHMDS gave the cyclopropane **7b** in quantitative yield (*cis*/*trans*=9). Although relative stereochemistries were not determined, both diastereomers of *trans* isomer derived from cyclopentene (*trans*-**6c**-1, *trans*-**6c**-2) showed almost equal reactivity in the cyclopropane formation to give only F-*endo* cyclopropane derivative **7c** in good yield (79 and 75%, respectively), while *cis* isomer (*cis*-**6c**-1 or *cis*-**6c**-2) gave the β-elimination product **8c**. This F-*endo* selective formation of the fluorocyclopropane carboxylate was also realized with *trans*-**6d** and *trans*-**6e** as shown in Scheme 3.

The following example indicates the efficiency of the present two-step preparation of fluorocyclopropane carboxylate. Triethylborane mediated atom-transfer radical addition of fluoroiodoacetate with 4-benzyloxycyclopentene **5f** proceeded at room temperature to give a isomeric mixture of the adduct **6f** in 76% yield. Without separation of isomers, the adduct **6f** was treated with LHMDS (5 equiv.) in THF at −78°C for 2 h to give the cyclopropane **7f** in 58% yield (2 steps) with complete F-*endo* selectivity (Scheme 4).

In conclusion, we have developed a convenient stereoselective preparation of 1-fluorocyclopropane-1-carboxylate derivatives including bicyclo[*n*.1.0] ring system through triethylborane mediated iodine atom-transfer radical addition of fluoroiodoacetate to 1-alkene or cyclic alkene followed by the subsequent cyclopropane formation via enolate of α-fluoro ester.

3. Experimental

^{1}H and ^{13}C NMR spectra were taken on a Brucker AM400 or a Varian Gemini-300 spectrometer, and chemical shifts were reported in parts per million (ppm) using $CHCl_3$ (7.26 ppm) in $CDCl_3$ for ^{1}H NMR, and $CDCl_3$ (77.01 ppm) for ^{13}C NMR as an internal standard, respectively. ^{19}F NMR spectra were taken on a Brucker AM400 spectrometer, and chemical shifts were reported in parts per million (ppm) using benzotrifluoride as a standard. Infrared spectra (IR) were recorded on a Perkin–Elmer FTIR-1710 infrared spectrophotometer. Mass spectra (MS) were obtained on a Hitachi M-80 or VG Auto spec. Medium pressure liquid chromatography (MPLC) was performed using prepacked column (silica gel, 50 μm) with UV or RI detector.

3.1. General procedure of triethylborane mediated addition of ethyl fluoroiodoacetate to alkenes: ethyl 2-fluoro-7-benzoyloxy-3-iodoheptanoate 6a

Under an argon atmosphere, to a mixture of **5a** (100 mg, 0.53 mmol) and ethyl fluoroiodoacetate[9] (180 mg, 0.78 mmol) in dichloromethane (3 ml) was added triethylborane (1 M hexane solution, 0.53 ml) at room temperature. Then, to the mixture was injected air (5 ml) by a syringe. After being stirred for 7 h at the same temperature, the reaction mixture was quenched by the addition of water and extracted with ether. The organic layer was washed with brine, dried over $MgSO_4$, then concentrated under reduced pressure. The residue was chromatographed on silica gel (hexane/ether=20:1) to give **6a** (195 mg, 88% yield, diastereomer ratio 1.7:1) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ; 8.05–8.01 (2H, m), 7.59–7.53 (1H, m), 7.47–7.41 (2H, m), 5.16 (0.63H, ddd, J=49.4, 10.8, 2.2 Hz, major-CFH), 5.09 (0.37H, ddd, J=48.6, 7.5, 5.0 Hz, minor-CFH), 4.39–4.23 (3H, m), 4.26 (2H, q, J=7.1 Hz), 2.65–1.85 (6H, m), 1.31 (3H, t, J=7.1 Hz). ^{19}F NMR (376.5 MHz, $CDCl_3$) δ; −127.6 (0.37F, ddd, J=48.6, 37.5, 19.3 Hz, minor), −131.9 (0.63F, ddd, J=49.4, 37.5, 12.5 Hz, major). EI-MS m/z: 423 ($M^{+}+1$). Anal. calcd for $C_{16}H_{20}FIO_4$: C, 45.51; H, 4.77. Found: C, 45.60; H, 4.82.

3.1.1. Ethyl 5-(*tert*-butyldiphenylsiloxy)-2-fluoro-4-iodopentanoate 6b. 73% yield, diastereomer ratio 1.1:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ; 7.67–7.64 (4H, m), 7.46–7.39 (6H, m), 5.13 (0.52H, ddd, J=49.5, 10.1, 3.1 Hz, major-CFH), 5.05 (0.48H, ddd, J=48.6, 7.8, 5.1 Hz, minor-CFH), 4.31–4.24 (3H, m), 3.91–3.85 (2H, m), 2.78–2.16 (2H, m), 1.32 (3H, t, J=7.1 Hz), 1.09 (9H, s). ^{19}F NMR (376.5 MHz, $CDCl_3$) δ; −128.0 (0.48F, ddd, J=48.6, 26.5, 18.5 Hz, minor), −131.6 (0.52F, ddd, J=49.5, 36.0, 14.5 Hz, major). EI-MS m/z: 529 ($M^{+}+1$). Anal. calcd for $C_{23}H_{30}FIO_3Si$: C, 52.27; H, 5.72. Found: C, 52.07; H, 5.68.

3.1.2. Ethyl 2-fluoro-2-(2-iodocyclopentyl)acetate 6c. In a similar manner, reaction of cyclopentene (0.18 ml, 2.0 mmol) with ethyl fluoroiodoacetate (120 mg, 0.52 mmol) in the presence of triethylborane (0.52 mmol) and the subsequent purification by column chromatography on silica gel (hexane/AcOEt=10:1) gave **6c** as a diastereomeric mixture, which was further separated by MPLC (hexane/AcOEt=9:1, flow rate 7.0 ml/min) to give *trans*-**6c**-1

(49 mg, 32% yield), *trans*-**6c**-2 (40 mg, 26% yield), *cis*-**6c**-1 (6.6 mg, 4% yield) and *cis*-**6c**-2 (9.6 mg, 6% yield) in the order of elution. *trans*-**6c**-1: ^{1}H NMR (400 MHz, CDCl$_3$) δ; 5.11 (1H, dd, J=49.4, 2.5 Hz), 4.27 (2H, q, J=7.2 Hz), 4.02 (1H, ddd, J=9.5, 9.5, 7.1 Hz), 2.63 (1H, dddd, J=32.0, 17.6, 9.1, 2.5 Hz), 2.41–2.29 (1H, m), 2.17–2.03 (1H, m), 1.31 (3H, t, J=7.2 Hz). ^{19}F NMR (376.5 MHz, CDCl$_3$) δ; −143.1 (1F, dd, J=49.4, 32.0 Hz). EI-MS m/z: 301 (M^{+}+1). HRMS calcd for $C_9H_{15}FIO_2$: 301.0101 (M^{+}+1), Found: 301.0114. *trans*-**6c**-2: ^{1}H NMR (400 MHz, CDCl$_3$) δ; 4.86 (1H, dd, J=48.3, 3.6 Hz), 4.30 (2H, q, J=7.2 Hz), 4.23 (1H, ddd, J=6.8, 6.8, 6.6 Hz), 2.88 (1H, ddddd, J=27.1, 9.9, 6.6, 6.6, 3.6 Hz), 2.23 (ddd, J=20.5, 6.8, 6.8 Hz), 2.21 (ddd, J=20.5, 6.8, 6.8 Hz), 2.00–1.58 (4H, m), 1.33 (3H, t, J=7.2 Hz). ^{19}F NMR (376.5 MHz, CDCl$_3$) δ; −136.5 (1F, dd, J=48.3, 27.0 Hz). EI-MS m/z: 301 (M^{+}+1). HRMS calcd for $C_9H_{15}FIO_2$: 301.0101 (M^{+}+1), Found: 301.0121. *cis*-**6c**-1: ^{1}H NMR (400 MHz, CDCl$_3$) δ; 4.97 (1H, dd, J=48.1, 6.5 Hz), 4.40 (1H, dd, J=9.2, 4.4 Hz), 4.23 (2H, m), 2.31–2.24 (2H, m), 2.05–1.60 (5H, m), 1.33 (3H, t, J=7.2 Hz). ^{19}F NMR (376.5 MHz, CDCl$_3$) δ; −132.2 (1F, dd, J=48.1, 16.0 Hz). EI-MS m/z: 301 (M^{+}+1). HRMS calcd for $C_9H_{14}FIO_2$: 300.0023 (M^{+}), Found: 300.0023. *cis*-**6c**-2: ^{1}H NMR (400 MHz, CDCl$_3$) δ; 4.76 (1H, dd, J=48.9, 9.7 Hz), 4.66 (1H, dd, J=4.2, 4.2 Hz), 2.36 (1H, ddd, J=14.6, 8.3, 1.6 Hz), 2.23 (dddd, J=14.3, 9.6, 9.6, 4.2 Hz), 2.15–2.00 (1H, m), 1.82–1.60 (3H, m), 1.53–1.41 (1H, m), 1.32 (3H, t, J=7.2 Hz). ^{19}F NMR (376.5 MHz, CDCl$_3$) δ; −123.0 (1F, dd, J=48.9, 9.0 Hz). EI-MS m/z: 301 (M^{+}+1). HRMS calcd for $C_9H_{14}FIO_2$: 300.0023 (M^{+}), Found: 300.0017.

3.1.3. Ethyl 2-fluoro-2-(4-iodotetrahydrofuran-3-yl)acetate 6d. A mixture of diastereomers obtained from **5d** (0.15 ml, 2.0 mmol), ethyl fluoroiodoacetate (120 mg, 0.52 mmol) and triethylborane (0.52 mmol) was separated by MPLC (hexane/AcOEt=4:1, flow rate 7.0 ml/min) to give *trans*-**6d**-1 (29 mg, 19% yield), *trans*-**6d**-2 (31 mg, 20% yield), *cis*-**6d**-1 (2.8 mg, 2% yield) and *cis*-**6d**-2 (3.6 mg, 2% yield) in the order of elution. *trans*-**6d**-1: ^{1}H NMR (400 MHz, CDCl$_3$) δ; 5.01 (1H, dd, J=48.6, 4.3 Hz), 4.29 (2H, q, J=7.1 Hz), 4.24 (1H, dd, J=8.9, 7.6 Hz), 4.14 (1H, dd, J=15.1, 7.6 Hz), 3.96–3.82 (3H, m), 2.97 (1H, dddd, J=25.6, 15.1, 7.6, 4.3 Hz), 1.33 (3H, t, J=7.1 Hz). ^{19}F NMR (376.5 MHz, CDCl$_3$) δ; −137.6 (1F, dd, J=48.6, 25.6 Hz). EI-MS m/z: 303 (M^{+}+1). HRMS calcd for $C_8H_{12}FO_3$: 175.0770 (M^{+}−I), Found: 175.0768. *trans*-**6d**-2: ^{1}H NMR (400 MHz, CDCl$_3$) δ; 4.87 (1H, dd, J=48.3, 4.5 Hz), 4.33 (2H, q, J=7.1 Hz), 4.28–4.17 (2H, m), 4.06 (1H, dd, J=9.2, 8.3 Hz), 3.97 (1H, dd, J=9.3, 6.3 Hz), 3.85 (dd, J=9.2, 5.7 Hz), 3.08 (dddd, J=23.0, 10.1, 8.3, 4.5 Hz), 1.35 (3H, t, J=7.1 Hz). ^{19}F NMR (376.5 MHz, CDCl$_3$) δ; −135.6 (1F, dd, J=48.3, 23.0 Hz). EI-MS m/z: 303 (M^{+}+1). HRMS calcd for $C_8H_{12}FO_3$: 175.0770 (M^{+}−I), Found: 175.0766. *cis*-**6d**-1: ^{1}H NMR (400 MHz, CDCl$_3$) δ; 5.12 (1H, dd, J=47.7, 6.4 Hz), 4.41 (2H, dd, J=11.2, 5.2 Hz), 4.36–4.26 (3H, m), 4.14 (1H, ddd, J=9.6, 5.2, 2.8 Hz), 4.06 (1H, dd, J=8.4, 7.8 Hz), 3.97 (dd, J=8.4, 7.8 Hz), 2.46 (ddddd, J=19.4, 9.6, 7.8, 7.8, 6.4 Hz), 1.33 (3H, t, J=7.2 Hz). ^{19}F NMR (376.5 MHz, CDCl$_3$) δ; −133.9 (1F, dd, J=47.7, 19.4 Hz). EI-MS m/z: 302 (M^{+}). HRMS calcd for $C_8H_{12}FO_3$: 175.0770 (M^{+}−I), Found: 175.0773. *cis*-**6d**-2: ^{1}H NMR (400 MHz, CDCl$_3$) δ; 4.91 (1H, dd, J=47.7, 10.1 Hz), 4.59 (2H, ddd, J=4.8, 2.3, 2.3 Hz), 4.40 (2H, d, J=2.3 Hz),4.35–4.23 (2H, m), 3.93 (1H, dd, J=8.5, 8.5 Hz), 3.84 (dd, J=9.6, 8.5 Hz), 1.96 (ddddd, J=10.1, 9.6, 8.7, 8.5, 4.8 Hz), 1.32 (3H, t, J=7.2 Hz). ^{19}F NMR (376.5 MHz, CDCl$_3$) δ; −125.7 (1F, dd, J=47.7, 8.7 Hz). EI-MS m/z: 302 (M^{+}). HRMS calcd for $C_8H_{12}FIO_3$: 301.9815 (M^{+}), Found: 301.9804.

3.1.4. Ethyl 2-fluoro-2-(2-iodocyclohexyl)acetate 6e. A diastereomeric mixture of the adduct **6e** (113 mg, 69% yield, *trans*-**6e**-1: *trans*-**6e**-2/*cis*-**6e**-1/*cis*-**6e**-2=3.5:5.8:1: 4.1) was separated by MPLC (hexane/AcOEt=12:1, flow rate 7.0 ml/min) to give *trans*-**6e**-1 (27 mg, 17% yield), *trans*-**6e**-2 (31 mg, 14% yield), *trans*-**6e**-2 and *cis*-**6e**-1 mixture (21 mg, 13% yield, *trans*-**6e**-2/*cis*-**6e**-1=1.7:1) and *cis*-**6e**-2 (32 mg, 15% yield) in the order of elution. *trans*-**6e**-1: ^{1}H NMR (400 MHz, CDCl$_3$) δ; 5.27 (1H, dd, J=46.5, 3.3 Hz), 4.50–4.19 (3H, m), 2.58–2.50 (1H, m), 2.28 (1H, ddddd, J=16.4, 11.4, 11.4, 3.5, 3.5 Hz), 2.10 (1H, ddd, J=25.2, 12.1, 3.7 Hz), 2.04–1.95 (1H, m), 1.88–1.81 (1H, m), 1.63–1.55 (1H, m), 1.45–1.23 (2H, m), 1.34 (3H, t, J=7.2 Hz), 1.18–1.05 (1H, m). ^{19}F NMR (376.5 MHz, CDCl$_3$) δ; −130.7 (1F, dd, J=46.5, 16.4 Hz). EI-MS m/z: 315 (M^{+}+1). Anal. calcd for $C_{10}H_{16}FIO_2$: C, 38.23; H, 5.13. Found: C, 38.33; H, 5.13. *trans*-**6e**-2: ^{1}H NMR (400 MHz, CDCl$_3$) δ; 5.40 (1H, dd, J=48.6, 1.8 Hz), 4.28 (2H, q, J=7.2 Hz), 4.21 (2H, ddd, J=11.9, 11.9, 4.2 Hz), 2.68–2.59 (1H, m), 2.27–2.08 (2H, m), 1.91–1.83 (1H, m), 1.62–1.23 (5H, m), 1.32 (3H, t, J=7.2 Hz). ^{19}F NMR (376.5 MHz, CDCl$_3$) δ; −144.8 (1F, dd, J=48.6, 3.1 Hz). EI-MS m/z: 315 (M^{+}+1). HRMS calcd for $C_3H_3FNO_3$: 314.0179 (M^{+}), Found: 314.0171. Anal. calcd for $C_{10}H_{16}FIO_2$: C, 38.23; H, 5.13. Found: C, 38.41; H, 5.15. *cis*-**6e**-1: ^{1}H NMR (400 MHz, CDCl$_3$) δ; 4.70 (1H, dd, J=48.4, 8.3 Hz), 4.58 (1H, br.s), 4.35–4.24 (2H, m), 2.27–1.25 (12H, m). ^{19}F NMR (376.5 MHz, CDCl$_3$) δ; −133.4 (1F, dd, J=48.4, 11.5 Hz). EI-MS m/z: 315 (M^{+}+1). HRMS calcd for $C_9H_{14}FIO_2$: 314.0179 (M^{+}), Found: 314.0168. *cis*-**6e**-2: ^{1}H NMR (400 MHz, CDCl$_3$) δ; 4.90 (1H, br.s), 4.60 (1H, dd, J=49.0, 9.8 Hz), 4.26 (2H, q, J=7.2 Hz), 2.24 (dddd, J=14.1, 5.0, 2.5, 2.5 Hz), 1.83–1.57 (4H, m), 1.48–1.23 (3H, m), 1.32 (3H, t, J=7.2 Hz), 1.07 (1H, dddd, J=19.0, 9.9, 4.0, 2.7 Hz). ^{19}F NMR (376.5 MHz, CDCl$_3$) δ; −130.6 (1F, dd, J=49.0, 9.9 Hz). EI-MS m/z: 315 (M^{+}+1). HRMS calcd for $C_9H_{14}FIO_2$: 314.0179 (M^{+}), Found: 314.0168.

3.2. General procedure of cyclopropane formation of fluoroiodo ester 6 with LHMDS: *cis* and *trans* ethyl 2-(3-benzoyloxypropyl)-1-fluorocyclopropane-1-carboxylate (*cis*-7a and *trans*-7a)

Under an argon atmosphere, to a solution of the fluoroiodo ester **6a** (isomer ratio 1.7:1, 100 mg, 0.24 mmol) in THF (2.5 ml) was added LHMDS (0.48 M THF-hexane solution, 1.6 ml, 0.76 mmol) prepared from n-BuLi and hexamethyldisilazane at −78°C. After being stirred for 3 h at the same temperature, the reaction mixture was quenched by the addition of 1N HCl and extracted with ether. The organic layer was washed with brine, dried over MgSO$_4$, then concentrated under reduced pressure. The residue was chromatographed on silica gel (hexane/AcOEt=10:1) to give **7a** as a diastereomeric mixture. The mixture was separated by

MPLC (hexane/AcOEt=6:1, flow rate 7.0 ml/min) to give *trans*-**7a** (8.5 mg, 12% yield) and *cis*-**7a** (48 mg, 69% yield), respectively. *trans*-**7a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ; 8.05–8.02 (2H, m), 7.57–7.52 (1H, m), 7.45–7.40 (2H, m), 4.34 (2H, t, *J*=6.4 Hz), 4.27 (2H, q, *J*=7.1 Hz), 1.87–1.68 (5H, m),1.57–1.46 (2H, m), 1.38–1.25 (1H, m), 1.31 (3H, t, *J*=7.1 Hz). ^{19}F NMR (376.5 MHz, $CDCl_3$) δ; −124.2 (1F, ddd, *J*=20.0, 20.0, 9.0 Hz). EI-MS *m/z*: 295 (M^++1). Anal. calcd for $C_{16}H_{19}FO_4$: C, 65.29; H, 6.51. Found: C, 65.16; H, 6.45. *cis*-**7a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ; 8.03–8.00 (2H, m), 7.55–7.50 (1H, m), 7.44–7.39 (2H, m), 4.35 (2H, t, *J*=6.4 Hz), 4.22 (2H, q, *J*=7.1 Hz), 1.92 (2H, tt, *J*=6.8, 6.4 Hz), 1.79–1.58 (1H, m), 1.51 (1H, ddd, *J*=9.8, 8.5, 6.2 Hz), 1.05 (1H, ddd, *J*=18.7, 7.7, 6.2 Hz), 1.31 (3H, t, *J*=7.1 Hz). ^{19}F NMR (376.5 MHz, $CDCl_3$) δ; −148.5 (1F, dd, *J*=18.7, 8.5 Hz). EI-MS *m/z*: 295 (M^++1). Anal. calcd for $C_{16}H_{19}FO_4$: C, 65.29; H, 6.51. Found: C, 65.43; H, 6.47.

3.2.1. Ethyl 2-(1-*tert*-butyldiphenylsiloxymethyl)-1-fluorocyclopropane-1-carboxylate 7b. Similarly, reaction of **6b** (130 mg, 0.25 mmol) with LHMDS (1.2 mmol) gave **7b** as a diastreomeric mixture, which was separated by MPLC (hexane/AcOEt=14:1, flow rate 7.0 ml/min) to give *trans*-**7b** (9.4 mg, 10% yield) and *cis*-**7b** (89 mg, 90% yield), respectively. *trans*-**7b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ; 7.67–7.62 (4H, m), 7.43–7.36 (6H, m), 4.25 (2H, q, *J*=7.2 Hz), 3.87 (1H, dd, *J*=11.3, 6.4 Hz), 3.66 (1H, dd, *J*=11.3, 8.9 Hz), 1.99 (1H, ddddd, *J*=17.8, 11.1, 10.9, 8.9, 6.4 Hz), 1.48 (1H, ddd, *J*=17.3, 10.9, 6.4 Hz), 1.35–1.26 (1H, m), 1.29 (3H, t, *J*=7.2 Hz), 1.03 (9H, s). ^{19}F NMR (376.5 MHz, $CDCl_3$) δ; −125.5 (1F, ddd, *J*=17.8, 17.3, 8.7 Hz). EI-MS *m/z*: 401 (M^++1). Anal. calcd for $C_{23}H_{29}FO_3Si$: C, 68.97; H, 7.30. Found: C, 68.97; H, 7.29. *cis*-**7b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ; 7.71–7.67 (4H, m), 7.46–7.36 (6H, m), 4.28 (2H, q, *J*=7.1 Hz), 3.91 (1H, dd, *J*=11.2, 5.7 Hz), 3.76 (1H, dd, *J*=11.2, 8.0 Hz), 1.93 (1H, dddd, *J*=10.5, 8.2, 8.1, 5.7 Hz), 1.48 (1H, ddd, *J*=10.5, 8.7, 6.4 Hz), 1.14 (1H, ddd, *J*=19.1, 8.2, 6.4 Hz), 1.32 (3H, t, *J*=7.1 Hz), 1.06 (9H, s). ^{19}F NMR (376.5 MHz, $CDCl_3$) δ; −147.9 (1F, dd, *J*=19.1, 8.7 Hz). EI-MS *m/z*: 401 (M^++1). HRMS calcd for $C_{19}H_{20}FO_3Si$: 343.1166 ($M^+-C_4H_9$), Found: 343.1184.

3.2.2. Ethyl 6-fluoro-bicyclo[3.1.0]hexane-6-carboxylate 7c. Colorless oil. 79% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ; 4.23 (2H, q, *J*=7.2 Hz), 2.15–1.95 (5H, m), 1.81–1.59 (3H, m), 1.30 (3H, t, *J*=7.2 Hz). ^{19}F NMR (376.5 MHz, $CDCl_3$) δ; −157.0 (1F, s). EI-MS *m/z*: 172 (M^+). HRMS calcd for $C_9H_{13}FO_2$: 172.0900 ($M^+-C_4H_9$), Found: 172.0902.

3.2.3. Ethyl 6-fluoro-3-oxabicyclo[3.1.0]hexane-6-carboxylate 7d and ethyl 7-fluoro-bicyclo[4.1.0]heptane-7-carboxylate 7e. ^{1}H and ^{19}F NMR spectra of these compounds were identical with those reported by Seyferth et al.[5a]

3.2.4. Ethyl cyclopent-1-yl-fluoroacetate 8c. Under an argon atmosphere, to a solution of the fluoroiodo ester *cis*-**6c**-2 (334 mg, 1.11 mmol) in THF (20 ml) was added LHMDS (0.48 M THF-hexane solution, 9.3 ml, 4.46 mmol) prepared from *n*-BuLi and hexamethyldisilazane at −78°C. After being stirred for 2 h at 0°C, the reaction mixture was quenched by the addition of 1N HCl and extracted with ether. The organic layer was washed with brine, dried over $MgSO_4$, then concentrated under reduced pressure. ^{1}H NMR spectrum of the residue using MeOH as an internal reference consisted of **8c** (45% yield) and the recovery of *cis*-**6c**-2 (5% yield). Purification by chromatography (SiO_2, pentane/ether=50:1) gave **8c** as a colorless oil. In a similar manner, *cis*-**6c**-1 (84 mg, 0.28 mmol) provided **8c** (20% yield) along with the recovery of *cis*-**6c**-1 (68% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ; 5.91 (1H, br.s), 5.39 (1H, d, *J*=48.5 Hz), 4.25 (2H, q, *J*=7.1 Hz), 2.49–2.25 (4H, m), 1.97–1.85 (2H, m), 1.29 (3H, t, *J*=7.1 Hz). ^{19}F NMR (376.5 MHz, $CDCl_3$) δ; −120.8 (1F, d, *J*=48.5 Hz). EI-MS *m/z*: 172 (M^+).

3.2.5. Ethyl 3-benzyloxy-6-fluoro-bicyclo[3.1.0]hexane-6-carboxylate 7f. Under an argon atmosphere, to a mixture of **5f** (360 mg, 2.1 mmol) and ethyl fluoroiodoacetate (120 mg, 0.52 mmol) in dichloromethane (2 ml) was added triethylborane (1 M hexane solution, 0.53 ml) at room temperature. Then, to the mixture was injected air (5 ml). After being stirred for 2 h at the same temperature, the reaction mixture was quenched by the addition of water and extracted with ether. The organic layer was washed with brine, dried over $MgSO_4$, then concentrated under reduced pressure. The residue was chromatographed on silica gel (hexane/ether=10:1) to give **6f** (160 mg, 76% yield, a diastereomeric mixture) as colorless oil. Under an argon atmosphere, to a solution of the fluoroiodo ester **6f** (110 mg, 0.27 mmol) in THF (3 ml) was added LHMDS (0.48 M THF–hexane solution, 2.9 ml, 1.4 mmol) prepared from *n*-BuLi and hexamethyldisilazane at −78°C. After being stirred for 2 h at the same temperature, the reaction mixture was quenched by the addition of 1N HCl and extracted with ether. The organic layer was washed with brine, dried over $MgSO_4$, then concentrated under reduced pressure. The residue was chromatographed on silica gel (hexane/AcOEt=10:1) to give **7f** as a diastreomeric mixture. Further purification by MPLC (hexane/AcOEt=6:1, flow rate 7.0 ml/min) gave **7f**-1 (23 mg, 30% yield) and **7f**-2 (34 mg, 45% yield), respectively. **7f**-1: colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ; 7.34–7.26 (5H, m), 4.45 (2H, s), 4.23 (2H, q, *J*=7.1 Hz), 4.04–3.96 (1H, m), 2.33 (2H, dd, *J*=13.5, 7.1 Hz), 2.20–2.08 (4H, m), 1.30 (3H, t, *J*=7.1 Hz). ^{19}F NMR (376.5 MHz, $CDCl_3$) δ; −153.9 (1F, s). EI-MS *m/z*: 279 (M^++1). HRMS calcd for $C_{16}H_{20}FO_3$: 279.1396 (M^++1), Found: 279.1394. **7f**-2: colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ; 7.34–7.26 (5H, m), 4.46 (2H, s), 4.36 (1H, ddd, *J*=16.5, 8.3, 8.3 Hz), 4.25 (2H, q, *J*=7.1 Hz), 2.53–2.31 (2H, m), 2.03–1.93 (2H, m), 1.77 (2H, dd, *J*=14.0, 8.3 Hz), 1.31 (3H, t, *J*=7.1 Hz). ^{19}F NMR (376.5 MHz, $CDCl_3$) δ; −153.7 (1F, s). EI-MS *m/z*: 279 (M^++1). HRMS calcd for $C_{16}H_{19}FO_3$: 278.1318 (M^+), Found: 278.1332.

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