Simmons–Smith Reactions of Fluoroallyl Alcohol Derivatives

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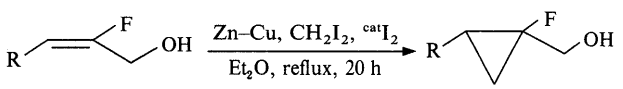
Simmons–Smith reactions of fluoroallyl alcohols and their derivatives with excess Zn–Cu and CH_2I_2 or Et_2Zn and CH_2I_2 provided fluorocyclopropane derivatives. Diastereoselective cyclopropanation of the fluoroallyl alcohol derivative obtained from (*R*)-2,3-*O*-isopropylidene glyceraldehyde was successfully carried out to give the optically active fluorocyclopropane derivative in high selectivity (>98% de).

Keywords Simmons–Smith reaction; cyclopropanation; fluorine; allyl alcohol; cyclopropane; diastereoselectivity; optically active

Organofluorine compounds have found many applications in bio- and medicinal chemistry and materials science, and recently the usefulness of the fluorocyclopropane moiety has been demonstrated in antibacterial substances and ferroelectric liquid crystals.[1] The Simmons–Smith reaction is extensively used in the synthesis of cyclopropane derivatives from olefins.[2] Functional groups on the double bond influence the reactivity of cyclopropanation of alkenes; electron-donating groups activate and electron-withdrawing groups deactivate the methylene-transfer reaction from the zinc reagent to alkenes. A fluorine-substituted double bond has been regarded as a deactivated substrate for Simmons–Smith reaction owing to the strong electron-withdrawing effect of the fluorine substituent. To our knowledge, no systematic study on the cyclopropanation of fluorine-substituted double bonds by Simmons–Smith reaction has been reported. It is well known that allylic oxygen in the Simmons–Smith reaction substrate accelerates the reaction rate of methylene transfer.[2a,3] Therefore, a fluorine-substituted double bond containing an allylic oxygen functionality would be expected to show enhanced reactivity toward the zinc reagent. Fluoroally alcohol derivatives ($-CH=CF-CH_2OH$) can be easily obtained by Horner–Emmons reaction of aldehydes with triethyl α-fluorophosphonoacetate followed by reduction.[4]

TABLE I. Reactions of Fluoroallyl Alcohol Derivatives with Zn–Cu and CH_2I_2



1 2

Entry	Substrate	eq of reagents (Zn–Cu/CH_2I_2)	Product (Yield, %)
1	**1a** (R=$PhCH_2CH_2$)	1.2/1.2	NR
2	**1b** (R=Ph)	1.2/1.2	NR
3	**1a**	5/5	**2a** (36)[a]
4	**1b**	5/5	**2b** (26)[a]
5	**1a**	5/5	**2a** (77)[b] (78)[b,c]
6	**1b**	5/5	**2b** (78)[b]
7	**1c** (R=cyclohexyl)	5/5	**2c** (75)[b]
8	**1a**	10/10	**2a** (78)[b]
9	**1a**	10/ 3	**2a** (68)[d] (65)[c,d]
10	**1a**	10/ 3	**2a** (57)[e]

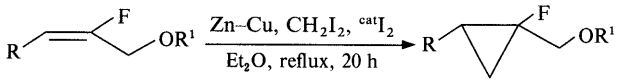
a) A mixture of acetal derivatives of **2a** or **2b** was also isolated. *b*) The crude reaction mixture was treated with HCl and MeOH. *c*) Irradiated with ultrasound. *d*) Reaction time was 10 h. *e*) Dimethoxyethane was used as the solvent.

In a continuation of our studies on fluorine-substituted cyclopropane derivatives,[5] we describe herein the cyclopropanation reactions of fluoroallyl alcohol derivatives by Simmons–Smith reaction, and also describe the synthesis of an optically active fluorocyclopropane derivative.

The results of reactions of fluoroallyl alcohol derivatives (**1**) with Zn–Cu, CH_2I_2, and a catalytic amount of I_2 in refluxing ether for 20 h are summarized in Table I. When 1.2 eq of the zinc reagent (Zn–Cu : CH_2I_2 = 1 : 1) was used, the cyclopropanation did not proceed at all and the starting materials were recovered (entries 1 and 2). The reactions of **1a** and **1b** with 5.0 eq of the zinc reagent gave the fluorocyclopropane derivatives (**2a** and **2b**) in 36% and 26% yields, respectively (entries 3 and 4). Scrambling at the hydroxyl group of cyclopropanes (**2a** and **2b**) by the formation of the mixture of acetal derivatives (*e.g.* formaldehyde acetal derivatives)[6] reduced the isolated yields of **2a** and **2b**. Treatment of the crude reaction mixture with HCl and MeOH for hydrolysis of acetal derivatives of cyclopropanes provided the corrected yields of the cyclopropanation: **2a** in 77% yield and **2b** in 78% yield (entries 5 and 6). Similarly, the cyclohexyl derivative (**1c**) yielded 75% of **2c** under the same conditions (entry 7). No difference in the yields of cyclopropanation was observed in the range from 5 to 10 eq of the zinc reagent (entries 5 and 8). By using the zinc reagent prepared *in situ* from 10 eq of Zn–Cu and 3 eq of CH_2I_2, side reactions (acetalizations) were suppressed and **2a** was obtained in 68% yield from **1a** without acidic hydrolysis (entry 9). Dimethoxyethane as a solvent provided a lower yield (57%) of **2a** (entry 10). Ultrasound irradiation of the reactant was not effective for increasing the yield of the cyclopropanation (entries 5 and 9).

Methoxymethyl (MOM) and benzyl (Bn) ether derivatives of fluoroallyl alcohols were also used as substrates for the reactions with Zn–Cu and CH_2I_2, as shown in Table II. The reaction of the MOM ether derivative (**3a**) with 5 eq of the zinc reagent gave a mixture of cyclopropanes in 40% combined yield; the MOM ether derivative of cyclopropane (**2a**) in 11% yield and a mixture of acetal derivatives of **2a**[6] in 29% yield (entry 1; the yield of 29% was determined after the hydrolysis of acetal derivatives to **2a** by treatment with HCl and MeOH). Thus, the MOM group in **3** was found to be unstable under the forced cyclopropanation conditions. Cyclopropanation of **3a** with 10 eq of the zinc reagent followed by hydrolysis with HCl and MeOH provided the alcohol derivative (**2a**) in 87%

TABLE II. Reactions of MOM and Bn Ether Derivatives of Fluoroallyl Alcohols with Zn–Cu and CH_2I_2

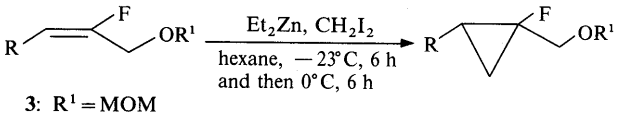


3: R^1 = MOM
4: R^1 = Bn
2: R^1 = H[a]
5: R^1 = Bn

Entry	Substrate	eq of reagents (Zn–Cu/CH_2I_2)	Product (Yield, %)
1	**3a** (R = $PhCH_2CH_2$)	5/5	**2a** (11 + 29)[b]
2	**3a**	10/10	**2a** (87)[a,c]
3	**3b** (R = Ph)	10/10	**2b** (26)[a,c]
4	**4a** (R = $PhCH_2CH_2$)	5/5	**5a** (47)
5	**4b** (R = Ph)	5/5	**5b** (12)
6	**4c** (R = cyclohexyl)	5/5	**5c** (39)
7	**4a**	10/10	**5a** (66)
8	**4b**	10/10	**5b** (44)
9	**4c**	10/10	**5c** (82)
10	**4d** [R = $PhCH_2CH_2CH(OH)$]	5/5	**5d** (39)

a) The crude reaction mixture was treated with HCl and MeOH. *b*) The isolated yield of the MOM ether derivative of **2a** was 11%, and the yield of the alcohol derivative (**2a**) obtained by the acidic hydrolysis of the isolated mixture of acetal derivatives of **2a** was 29%. *c*) Reaction time was 40 h.

TABLE III. Reactions of MOM and Bn Ether Derivatives of Fluoroallyl Alcohols with Et_2Zn and CH_2I_2



3: R^1 = MOM
4: R^1 = Bn
5: R^1 = Bn

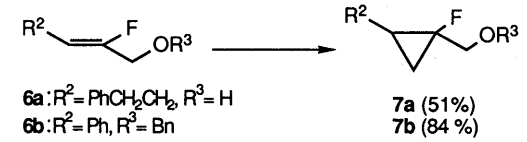
Entry	Substrate	eq of reagents (Et_2Zn/CH_2I_2)	Product (Yield, %)
1	**3a**	5/10	NR
2	**3b**	5/10	NR
3	**4a**	5/10	**5a** (41)
4	**4b**	5/10	**5b** (3)
5	**4c**	5/10	NR
6	**4a**	7.5/15	**5a** (70)[a]
7	**4b**	7.5/15	**5b** (31)[a]
8	**4c**	7.5/15	**5c** (34)[a]

a) Reaction time was 6 h (−23 °C) and then 16 h (0 °C).

yield (entry 2). Benzyl ether derivatives (**4a—c**) gave the fluorocyclopropanes (**5a—c**) in 12—47% yields with 5 eq of the zinc reagent (entries 4—6). Further excess of the zinc reagents (10 eq) provided higher yields (44—82%) of **5a—c** (entries 7—9). In contrast to the case of the fluoroallyl alcohol derivative (Table I, entry 6), cyclopropanation of the phenyl-substituted benzyl ether derivative (**4b**) provided a lower yield of **5b** (Table II, entries 5 and 8).

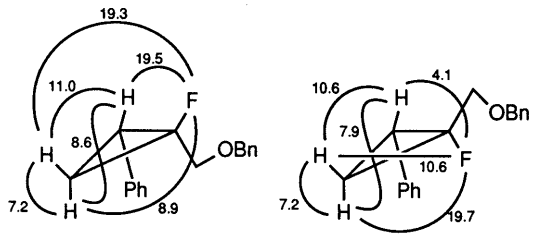
The cyclopropanation using Et_2Zn and CH_2I_2 was studied, with the results shown in Table III. No cyclopropanation reaction of MOM ether derivatives (**3a** and **3b**) occurred with 5 eq of Et_2Zn and 10 eq of CH_2I_2 (entries 1 and 2). The benzyl ether derivative (**4a**) gave **5a** in 41% yield under the same conditions (entry 3). By increasing the amount of zinc reagent, 31—70% yields of the cyclopropanes (**5a—c**) were obtained (entries 6—8).

In the cyclopropanation reactions of the (*E*)-fluoroallyl alcohol derivatives described above, the *cis* [with respect to R- and $R^1(H)OCH_2$-]-fluorocyclopropane was obtained



6a: R^2 = $PhCH_2CH_2$, R^3 = H
6b: R^2 = Ph, R^3 = Bn
7a (51%)
7b (84 %)

reaction conditions: ^{5eq}Zn-Cu, $^{5eq}CH_2I_2$, ether, reflux, 20 h, and then HCl - MeOH for **6a**; ^{10eq}Zn-Cu, $^{10eq}CH_2I_2$, ether, reflux, 20 h for **6b**



5b (*cis*) **7b** (*trans*)

J-values(Hz) of *cis*- and *trans*-fluorocyclopropanes in the ^{1}H-NMR spectra

Chart 1

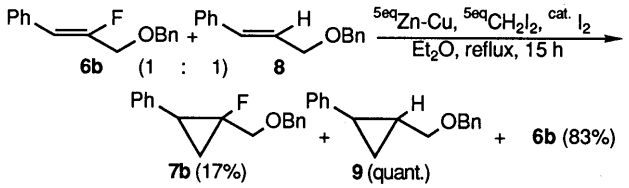
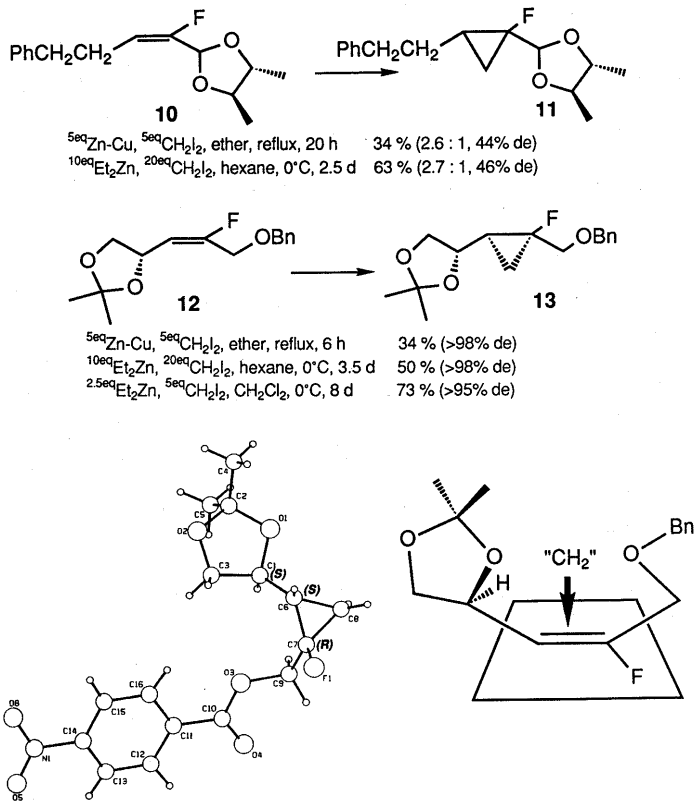


Chart 2

stereoselectively. The complete stereospecificity of the cyclopropanation was confirmed by the reaction of (*Z*)-fluoroallyl alcohol derivatives (**6a** and **6b**), giving *trans* (with respect to R^2- and R^3OCH_2-)-fluorocyclopropane derivatives (**7a** and **7b**). Characteristic *J*-values of the *cis* and *trans*-fluorocyclopropanes (**5b** and **7b**) in the ^{1}H-NMR spectra are shown in Chart 1.

In order to estimate the effect of a fluorine substituent on the double bond in the Simmons–Smith reaction, competitive cyclopropanation of the benzyl ether derivatives of fluoroallyl alcohol (**6b**) *versus* fluorine-free allyl alcohol (**8**) was examined (Chart 2). When a mixture (1 eq) of equimolar **6b** and **8** was reacted with the zinc reagent (5 eq), the products were **7b** (17% yield), **9** (quantitative yield), and recovered **6b** (83% yield). Thus, the fluorine substituent strongly deactivated the double bond even in the allylic alcohol system toward the methylene-transfer reaction with the zinc reagent.

Asymmetric cyclopropanation of fluoro-olefin derivatives was also examined (Chart 3).[7] Substrates containing a chiral dioxolane ring (**10**) and protected chiral allyl alcohol moiety (**12**) were prepared. Reaction of **10** containing the homochiral acetal group with Zn–Cu and CH_2I_2 gave a 2.6 : 1 mixture (44% de) of diastereomeric fluorocyclopropane (**11**) in 34% yield. Although the chemical yield of **11** was improved to 63% on treatment of **10** with 10 eq of Et_2Zn and 20 eq of CH_2I_2, no appreciable change in diastereoselectivity was observed (2.7 : 1, 46% de). The direction of diastereoselectivity of the methylene-transfer was not determined. Highly diastereoselective cyclopropanation was observed with **12**, derived from (*R*)-2,3-*O*-isopropylidene glyceraldehyde. Thus, **12** gave **13**



stereostructure of *p*-nitrobenzoyl derivative of **13** determined by X-ray crystallographic analysis

Chart 3

in over 98% de (determined by GLC) in the reaction with Zn–Cu and CH_2I_2 (34% yield) or Et_2Zn and CH_2I_2 (50% yield). When cyclopropanation reaction was carried out with 2.5 eq of Et_2Zn and 5 eq of CH_2I_2 in CH_2Cl_2 at 0 °C for 8 d, **13** was obtained in higher yield (73%, >95% de). The absolute stereochemistry of **13** was established as (1*R*, 2*S*, 1′*S*) by X-ray crystallographic analysis of its *p*-nitrobenzoyl derivative. The stereochemistry of the diastereoselective methylene-transfer to **12** is depicted in Chart 3. Complexation of the zinc reagent with ethereal oxygen(s) seems to control the π-facial selectivity in the methylene-transfer process.[8)]

In summary, cyclopropanation reactions of fluoroallyl alcohol derivatives proceeded with a large excess of the zinc reagent prepared *in situ* from Zn–Cu and CH_2I_2 or Et_2Zn and CH_2I_2. An optically active fluorocyclopropane (**13**) was synthesized with high diastereoselectivity by the reaction of a fluoroallyl alcohol derivative obtained from (*R*)-2,3-*O*-isopropylidene glyceraldehyde with the zinc reagent. The present reaction provides a useful method for preparing fluorocyclopropane derivatives.

Experimental

^{1}H-NMR spectra were taken on a Brucker AM400 or a Varian Gemini-300 spectrometer in $CDCl_3$. ^{19}F-NMR spectra were taken on a Brucker AM400 or a Varian EM360L spectrometer in $CDCl_3$, and chemical shifts are reported as ppm relative to benzotrifluoride as the internal standard. Infrared (IR) spectra were recorded on a Perkin-Elmer FTIR-1710 infrared spectrophotometer. Mass spectra (MS) were obtained on a Hitachi M-80 or a VG Auto Spec. Optical rotations were measured with a JASCO DIP-360 digital polarimeter. Zinc-copper couple was prepared from zinc and copper sulfate by the method described in *Org. Reac.* (ref. 2*a*, p. 82). All reactions were conducted under an argon atmosphere.

Typical Procedure for the Preparation of Fluoroallyl Alcohol Derivatives A solution of triethyl α-fluorophosphonoacetate [$(EtO)_2POCHFCO_2Et$, 8.9 g, 36.9 mmol] in tetrahydrofuran (THF, 20 ml) was cooled to −78 °C, and a solution of sodium bis(trimethylsilyl)amide (1.0 M solution in THF, 37 ml, 37 mmol) was added. The mixture was kept for 30 min at −78 °C, then a solution of β-phenylpropionaldehyde ($PhCH_2CH_2CHO$, 4.5 g, 33.5 mmol) in THF (30 ml) was added. After being stirred for 1 h at −78 °C, the reaction mixture was treated with aqueous NH_4Cl and extracted with ether. The ether phase was washed with saturated aqueous NaCl and dried over $MgSO_4$. The residue upon work-up was chromatographed on silica gel to give ethyl (*E*)-5-phenyl-2-fluoropent-2-enoate ($PhCH_2CH_2CH=CFCO_2Et$, 5.71 g, 77% yield). The (*Z*)-isomer was also obtained as minor component (yield not determined). A solution of ethyl (*E*)-5-phenyl-2-fluoropent-2-enoate (1.26 g, 5.68 mmol) in ether (10 ml) was cooled to −78 °C, and diisobutylaluminum hydride (DIBAL-H, 1.0 M solution in hexane, 11.4 ml, 11.4 mmol) was added. After being stirred for 2 h at 78 °C, the reaction mixture was treated with saturated aqueous NaCl and then filtered through Celite. The ether phase was washed with saturated aqueous NaCl and dried over $MgSO_4$. The residue upon work-up was chromatographed on silica gel to give (*E*)-5-phenyl-2-fluoropent-2-en-1-ol (**1a**, 0.95 g, 93% yield). Methoxymethyl (MOM) and benzyl (Bn) ether derivatives were obtained by the standard methods (MOMCl or BnBr and NaH in THF).

Preparation of 10 and 12 A solution of ethyl (*E*)-5-phenyl-2-fluoropent-2-enoate (2.57 g, 11.58 mmol) in ether (15 ml) was cooled to −78 °C, and DIBAL-H (1.0 M solution in hexane, 12.2 ml, 12.2 mmol) was added. After being stirred for 1 h at −78 °C, the reaction mixture was treatd with saturated aqueous NaCl and then filtered through Celite. The ether phase was washed with saturated aqueous NaCl and dried over $MgSO_4$. The residue upon work-up was chromatographed on silica gel to give (*E*)-5-phenyl-2-fluoropent-2-enal (1.58 g, 77% yield). A mixture of (*E*)-5-phenyl-2-fluoropent-2-enal (1.577 g, 8.86 mmol), (2*R*, 3*R*)-(−)-2,3-butanediol (878.5 mg, 9.75 mmol), and pyridinium *p*-toluenesulfonate (catalytic amount) in benzene (30 ml) was stirred at reflux temperature for 4 h with azeotropic removal of water using molecular sieves. The reaction mixture was neutralized with aqueous $NaHCO_3$ and extracted with ether. The ether phase was washed with saturated aqueous $NaHCO_3$ and NaCl, and dried over $MgSO_4$. The residue upon work-up was chromatographed on silica gel to give **10** (2.16 g, 97% yield). $[\alpha]_D^{27}$ −19.6° (c=1.04, $CHCl_3$). ^{1}H-NMR δ: 1.27 (3H, d, J=6.0 Hz, CH_3), 1.32 (3H, d, J=6.0 Hz, CH_3), 2.41 (2H, dt, J=8.2, 7.4 Hz, CH_2), 2.71 (2H, t, J=7.4 Hz, CH_2Ph), 3.59—3.81 (2H, m, CH×2), 5.38 (1H, dt, J=20.9, 8.2 Hz, CH=), 5.77 (1H, d, J=21.7 Hz, O–CH–O), 7.16—7.32 (5H, m, aromatic H). ^{19}F-NMR δ: −63.2 (1F, dd, J=21.7, 20.9 Hz). With the same procedure as described above, (*R*)-2,3-*O*-isopropylidene glyceraldehyde (4.0 g, 30.8 mmol) was reacted with $(EtO)_2POCHFCO_2Et$ (8.19 g, 33.9 mmol) and sodium bis(trimethylsilyl)amide (1.0 M solution in THF, 33.9 ml, 33.9 mmol) to give the α-fluoro-α,β-unsaturated ester derivative (6.04 g, 90% yield), which was converted to **12** by treatment with DIBAL-H (98% yield) followed by BnBr and NaH (85% yield). $[\alpha]_D^{27}$ −38.3° (c=2.03, $CHCl_3$). ^{1}H-NMR δ: 1.36 (3H, s, CH_3), 1.41 (3H, s, CH_3), 3.58 (1H, dd, J=8.1, 7.5 Hz, CH–O), 4.05 (1H, dd, J=8.1, 6.1 Hz, CH–O), 4.11 (1H, dd, J=18.7, 13.2 Hz, CH–O), 4.21 (1H, dd, J=22.0, 13.2 Hz, CH–O), 4.55 (1H, d, J=12.0 Hz, PhCH-O), 4.59 (1H, d, J=12.0 Hz, PhCH–O), 4.64 (1H, dddd, J=9.4, 7.5, 6.1, 1.7 Hz, CH–O), 5.35 (1H, dd, J=19.0, 9.4 Hz, CH=), 7.29—7.38 (5H, m, aromatic H). ^{19}F-NMR δ: −39.3 (1F, dddd, J=22.0, 19.0, 18.7, 1.7 Hz).

Typical Procedure for the Cyclopropanation Reaction with Zn–Cu and CH_2I_2 (Table I. Entry 9) A mixture of zinc-copper couple (361.4 mg, 5.6 g-atom), diiodomethane (446.7 mg, 1.67 mmol), iodine (catalytic amount), and fluoroallyl alcohol derivative (**1a**, 100 mg, 0.56 mmol) in ether (5 ml) was stirred at reflux temperature for 10 h. The reaction mixture was diluted with ether, treated with aqueous NH_4Cl, and then filtered through Celite. The ether phase was washed with saturated aqueous $NaHCO_3$ and NaCl, and dried over $MgSO_4$. The residue upon work-up was chromatographed on silica gel to give the fluorocyclopropane derivative (**2a**, 73.4 mg, 68% yield). In the reactions of entries 5—8 in Table I and entries 2 and 3 in Table II, hydrolysis of the crude reaction mixture was carried out as follows: after the work-up described above, a solution of the crude reaction mixture (*ca.* 1 mmol scale) and hydrochloric acid (25 μl) in MeOH (2.5 ml) was stirred at 60 °C for 3 h. The reaction mixture was neutralized with aqueous $NaHCO_3$ and extracted with ether. The ether phase was washed with saturated aqueous $NaHCO_3$ and NaCl, and dried over $MgSO_4$. The residue upon work-up was chromatographed

on silica gel to give fluorocyclopropane derivatives (**2**).

Typical Procedure for the Cyclopropanation Reaction with Et_2Zn and CH_2I_2 (Table III. Entry 6) A solution of fluoroallyl alcohol derivative (**4a**, 52 mg, 0.19 mmol) in hexane (3 ml) was cooled to −23 °C, and diethyl zinc (1.0 M solution in hexane, 1.44 ml, 1.44 mmol) and diiodomethane (763 mg, 2.85 mmol) were added. After being stirred vigorously for 6 h at −23 °C and 16 h at 0 °C, the reaction mixture was treated with aqueous NH_4Cl and extracted with ether. The ether phase was washed with saturated aqueous $NaHCO_3$ and NaCl, and dried over $MgSO_4$. The residue upon work-up was chromatographed on silica gel to give the fluorocyclopropane derivative (**5a**, 38.0 mg, 70% yield).

Spectral Data of Fluorocyclopropanes. 1-Fluoro-1-hydroxymethyl-2-(2-phenylethyl)cyclopropane (2a) ^{1}H-NMR δ: 0.40 (1H, ddd, J=8.7, 7.1, 6.8 Hz, CH), 1.18 (1H, dddd, J=19.8, 10.7, 6.8, 1.0 Hz, CH), 1.35—1.58, 1.71—1.80 (4H, m, CH_2, CH, OH), 2.75 (2H, t, J=7.5 Hz, $PhCH_2$), 3.75 (1H, ddd, J=26.6, 13.3, 1.0 Hz, CH–O), 3.95 (1H, dd, J=21.7, 13.3 Hz, CH–O), 7.18—7.31 (5H, m, aromatic H). ^{19}F-NMR δ: −118.2 (1F, m). IR (neat): 3369, 3063, 3027, 2930, 2861, 1604, 1497, 1455 cm^{-1}. MS m/z: 194 (M^+), 176, 161, 143, 129, 117, 91. High-resolution MS m/z: Calcd for $C_{12}H_{15}FO$: 194.1107. Found: 194.1128.

1-Fluoro-1-hydroxymethyl-2-phenylcyclopropane (2b) ^{1}H-NMR δ: 1.28 (1H, ddd, J=8.9, 7.9, 7.3 Hz, CH), 1.56 (1H, ddd, J=19.3, 10.9, 7.3 Hz, CH), 1.61 (1H, br, OH), 2.75 (1H, ddd, J=19.9, 10.9, 7.9 Hz, PhCH), 3.69 (2H, d, J=23.0 Hz, CH_2–O), 7.21—7.33 (5H, m, aromatic H). ^{19}F-NMR δ: −116.6 (1F, tddd, J=23.0, 19.9, 19.3, 8.9 Hz). IR (neat): 3370, 3062, 3029, 2931, 1605, 1499, 1456 cm^{-1}. MS m/z: 166 (M^+), 147, 135, 115. High-resolution MS m/z: Calcd for $C_{10}H_{11}FO$: 166.0794. Found: 166.0772.

2-Cyclohexyl-1-fluoro-1-hydroxymethylcyclopropane (2c) ^{1}H-NMR δ: 0.39 (1H, ddd, J=9.0, 7.0, 6.9 Hz, CH), 0.63—0.70 (1H, m, CH), 1.01—1.28, 1.63—1.88 (13H, m, CH_2×5, CH×2, OH), 3.91 (1H, d, J=24.0 Hz, CH_2–O). ^{19}F-NMR δ: −116.3 (1F, tddd, J=24.0, 22.3, 19.9, 9.0 Hz). IR (neat): 3370, 2926, 2852, 1450 cm^{-1}. MS m/z: 154 ($M^+ - H_2O$).

MOM Ether Derivative of 2a ^{1}H-NMR δ: 0.42 (1H, ddd, J=8.6, 7.1, 7.1 Hz, CH), 1.20 (1H, dddd, J=19.5, 10.7, 7.1, 1.0 Hz, CH), 1.36—1.53 (2H, m, CH, CH), 1.75—1.84 (1H, m, CH), 2.75 (2H, t, J=7.5 Hz, CH_2), 3.38 (3H, s, CH_3), 3.72 (1H, ddd, J=27.1, 12.4, 1.0 Hz, CH–O), 3.89 (1H, dd, J=22.0, 12.4 Hz, CH–O), 4.69 (1H, d, J=6.6 Hz, O–CH–O), 4.72 (1H, d, J=6.6 Hz, O–CH–O), 7.18—7.30 (5H, m, aromatic H). ^{19}F-NMR δ: −114.86 (1F, m). IR (neat): 3063, 3027, 3001, 2931, 1732, 1604, 1497, 1455 cm^{-1}. MS m/z: 238 (M^+), 218, 193, 173. High-resolution MS m/z: Calcd for $C_{14}H_{19}FO_2$: 238.1369. Found: 238.1366.

1-Benzyloxymethyl-1-fluoro-2-(2-phenylethyl)cyclopropane (5a) ^{1}H-NMR δ:0.40 (1H, ddd, J=8.5, 6.8, 6.8 Hz, CH), 1.18 (1H, ddd, J=19.7, 10.4, 6.8 Hz, CH), 1.35—1.50 (2H, m, CH, CH), 1.68—1.79 (1H, m, CH), 2.74 (2H, t, J=7.8 Hz, $PhCH_2$), 3.62 (1H, dd, J=27.8, 12.3 Hz, CH–O), 3.84 (1H, dd, J=21.3, 12.3 Hz, CH–O), 4.59 (1H, d, J=12.1 Hz, PhCH–O), 4.66 (1H, d, J=12.1 Hz, PhCH–O), 7.15—7.37 (10H, m, aromatic H). ^{19}F-NMR δ: −113.3 (1F, m). IR (neat): 3063, 3028, 2927, 2860, 1604, 1496, 1454 cm^{-1}. MS m/z: 284 (M^+), 207, 193, 175, 155, 91. High-resolution MS m/z: Calcd for $C_{19}H_{21}FO$: 284.1576. Found: 284.1560.

1-Benzyloxymethyl-1-fluoro-2-phenylcyclopropane (5b) ^{1}H-NMR δ: 1.27 (1H, ddd, J=8.9, 8.6, 7.2 Hz, CH), 1.58 (1H, dddd, J=19.3, 11.0, 7.2, 1.2 Hz, CH), 2.73 (1H, ddd, J=19.5, 11.0, 8.6 Hz, CH), 3.51 (1H, dd, J=23.7, 12.2 Hz, CH–O), 3.59 (1H, ddd, J=23.6, 12.2, 1.2 Hz, CH–O), 4.43 (1H, d, J=12.2 Hz, PhCH–O), 4.47 (1H, d, J=12.2 Hz, PhCH–O), 7.17—7.30 (10H, m, aromatic H). ^{19}F-NMR δ: −111.9 (1F, m). IR (neat): 3062, 3030, 2859, 1605, 1498, 1454 cm^{-1}. MS m/z: 256 (M^+), 197, 135, 91. High-resolution MS m/z: Calcd for $C_{17}H_{17}FO$: 256.1263. Found: 256.1280.

1-Benzyloxymethyl-2-cyclohexyl-1-fluorocyclopropane (5c) ^{1}H-NMR δ: 0.39 (1H, ddd, J=8.8, 7.2, 6.6 Hz, CH), 0.59—0.64 (1H, m, CH), 1.00—1.94 (12H, m, CH_2×5, CH×2), 3.76 (1H, dd, J=23.6, 15.5 Hz, CH–O), 3.80 (1H, dd, J=23.6, 15.5 Hz, CH–O), 4.59 (1H, d, J=12.2 Hz, PhCH–O), 4.69 (1H, d, J=12.2Hz, PhCH–O), 7.27—7.37 (5H, m, aromatic H). ^{19}F-NMR δ: −111.4 (1F, ddddd, J=23.6, 23.6, 23.6, 23.6, 8.8 Hz). IR (neat): 3065, 3031, 2998, 2924, 2851, 1497, 1451 cm^{-1}. MS m/z: 262 (M^+), 91. High-resolution MS m/z: Calcd for $C_{17}H_{23}FO$: 262.1733. Found: 262.1732.

1-Benzyloxymethyl-1-fluoro-2-(1-hydroxy-3-phenylpropyl)cyclopropane (5d) ^{1}H-NMR δ: 0.76 (1H, ddd, J=8.1, 7.5, 6.7 Hz, CH), 1.22 (1H, ddd, J=19.0, 11.0, 6.7 Hz, CH), 1.62 (2H, dddd, J=21.5, 11.0, 8.0, 7.5 Hz, CH, br, OH), 1.88 (1H, dddd, J=13.4, 9.5, 9.0, 5.2 Hz, CH), 2.02 (1H, dddd, J=13.4, 9.8, 7.0, 3.6 Hz, CH), 2.68 (1H, ddd, J=13.8, 9.5, 7.0 Hz, PhCH), 2.83 (1H, ddd, J=13.8, 9.8, 5.2 Hz, PhCH), 3.42 (1H, ddd, J=9.0, 8.0, 3.6 Hz, CH–O), 3.62 (1H, dd, J=30.8, 12.2 Hz, CH–O), 3.98 (1H, dd, J=19.2, 12.2 Hz, CH–O), 4.53 (1H, d, J=12.0 Hz, PhCH–O), 4.62 (1H, J=12.0 Hz, PhCH–O), 7.16—7.37 (10H, m, aromatic H). ^{19}F-NMR δ: −109.8 (1F, ddddd, J=30.8, 21.5, 19.2, 19.0, 8.1 Hz). IR (neat): 3421, 3086, 3062, 3028, 2922, 2861, 1603, 1496, 1454 cm^{-1}. MS m/z: 296 ($M^+ - H_2O$), 223, 205, 185. High-resolution MS m/z: Calcd for $C_{20}H_{21}FO$ ($M^+ - H_2O$): 296.1576. Found; 296.1568.

1-Fluoro-1-hydroxymethyl-2-(2-phenylethyl)cyclopropane (7a) ^{1}H-NMR δ: 0.73 (1H, ddd, J=13.9, 13.0, 6.6 Hz, CH), 0.83 (1H, ddd, J=9.7, 9.3, 6.6 Hz, CH), 0.88—0.96 (1H, m, CH), 1.62 (1H, br, OH), 1.76—1.93 (2H, m, CH_2), 2.75 (2H, t, J=7.6 Hz, $PhCH_2$), 3.70 (1H, dd, J=23.1, 12.9 Hz, CH), 3.79 (1H, dd, J=22.0, 12.9 Hz, CH), 7.17—7.31 (5H, m, aromatic H). ^{19}F-NMR δ: −141.9 (1F, m). IR (neat): 3368, 3063, 3027, 3002, 2927, 2863, 1604, 1496, 1455 cm^{-1}. MS m/z: 194 (M^+), 129, 117, 91. High-resolution MS m/z: Calcd for $C_{12}H_{15}FO$: 194.1107. Found: 194.1114.

1-Benzyloxymethyl-1-fluoro-2-phenylcyclopropane (7b) ^{1}H-NMR δ: 1.31 (1H, ddd, J=10.6, 10.6, 7.2 Hz, CH), 1.51 (1H, dddd, J=19.7, 7.9, 7.2, 0.9 Hz, CH), 2.22 (1H, ddd, J=10.6, 7.9, 4.1 Hz, CH), 3.83 (1H, ddd, J=21.2, 11.9, 0.9 Hz, CH–O), 3.87 (1H, dd, J=20.9, 11.9 Hz, CH–O), 4.69 (2H, s, $PhCH_2$), 7.23—7.41 (10H, m, aromatic H). ^{19}F-NMR δ: −133.94 (1F, ddddd, J=21.2, 20.9, 19.7, 10.6, 4.1 Hz). IR (neat): 3063, 3029, 2861, 1605, 1499, 1454 cm^{-1}. MS m/z: 256 (M^+), 197, 145, 91. High-resolution MS m/z: Calcd for $C_{17}H_{17}FO$: 256.1263. Found: 256.1259.

1-(4,5-Dimethyl-1,3-dioxa-2-olanyl)-1-fluoro-2-(2-phenylethyl)cyclopropane (11) Mixture of diastereoisomers (2.6:1 or 2.7:1 determined by GLC). ^{1}H-NMR δ: 0.56—0.65 (1H, m, CH), 1.20—1.57 (3H, m, CH×3), 1.27 (3H, d, J=6.0 Hz, CH_3), 1.34 (3H, d, J=6.0 Hz, CH_3), 1.81—1.89 (1H, m, CH), 2.70—2.80 (2H, m, CH_2), 3.62—3.82 (2H, m, CH–O×2), 4.95 (1H for major isomer, d, J=20.3 Hz, O–CH–O), 4.98 (1H for minor isomer, d, J=19.4 Hz, O–CH–O), 7.15—7.30 (5H, m, aromatic H). ^{19}F-NMR δ: −131.1 (for minor isomer), 132.0 (for major isomer) (1F, each m). IR (neat): 3063, 3027, 2975, 2931, 1604, 1497, 1455 cm^{-1}. MS m/z: 264 (M^+), 91. High-resolution MS m/z: Calcd for $C_{16}H_{21}FO_2$: 264.1526. Found: 264.1546.

(1*R*,2*S*,1′*S*)-1-Benzyloxymethyl-1-fluoro-2-(1,2-*O*-isopropylidene-1,2-dihydroxyethyl)cyclopropane (13) The diastereoselectivity (>98% de) was determined by GLC. $[\alpha]_D^{27}$ −46.1° (c=0.25, $CHCl_3$). ^{1}H-NMR δ: 0.84 (1H, ddd, J=8.9, 7.3, 7.2 Hz, CH), 1.31 (3H, s, CH_3), 1.33 (1H, ddd, J=19.1, 10.8, 7.1 Hz, CH), 1.42 (3H, s, CH_3), 1.59 (1H, dddd, J=20.5, 14.0, 10.8, 7.3 Hz, CH), 3.52 (1H, dd, J=32.9, 12.3 Hz, CH–O), 3.68 (1H, ddd, J=14.0, 7.3, 6.0, CH–O), 3.79 (1H, dd, J=8.3, 7.3 Hz, CH–O), 4.09 (1H, dd, J=17.8, 12.3 Hz, CH–O), 4.15 (1H, dd, J=8.3, 6.0 Hz, CH–O), 4.54 (1H, d, J=12.0 Hz, PhCH–O), 4.66 (1H, d, J=12.0 Hz, PhCH–O), 7.28—7.38 (5H, m, aromatic H). ^{19}F-NMR δ: −112.75 (1F, ddddd, J=32.9, 20.5, 19.1, 17.8, 8.9 Hz). IR (neat): 3031, 2986, 2933, 2870, 1497, 1455 cm^{-1}. MS m/z: 281 (M^++1), 265, 222. High-resolution MS m/z: Calcd for $C_{16}H_{21}FO_3$: 280.1475. Found: 280.1461.

***p*-Nitrobenzoyl Derivative of 13** The *p*-nitrobenzoyl derivative of **13** for X-ray crystallographic analysis was obtained by the deprotection of the Bn group (H_2, 5% Pd–C, EtOH) followed by esterification (*p*-nitrobenzoyl chloride, Et_3N, CH_2Cl_2). mp 110.5—113 °C (recrystallized from hexane–ether). $[\alpha]_D^{25}$ −63.2° (c=1.00, $CHCl_3$). ^{1}H-NMR δ: 1.08 (1H, ddd, J=9.0, 7.5, 7.0 Hz, CH), 1.30 (3H, s, CH_3), 1.41 (3H, s, CH_3), 1.42 (1H, dddd, J=18.9, 11.0, 7.0, 0.9 Hz, CH), 1.70 (1H, m, CH), 3.75 (1H, dd, J=7.9, 7.4 Hz, CH–O), 4.11 (1H, dd, J=7.9, 6.1 Hz, CH–O), 4.56 (1H, ddd, J=28.5, 13.2, 0.9 Hz, CH–O), 4.99 (1H, ddd, J=20.5, 13.2, 0.7 Hz, CH–O), 8.24–8.33 (4H, m, aromatic H). *Anal.* Calcd for $C_{16}H_{18}FNO_6$: C, 56.64; H, 5.35; N, 4.13. Found: C, 56.68; H, 5.33; N, 4.23.

References and Notes

1) *a*) O. Tamura, M. Hashimoto, Y. Kobayashi, T. Katoh, K. Nakatani, M. Kamada, I. Hayakawa, T. Akiba, and S. Terashima, *Tetrahedron Lett.*, **33**, 3483, 3487 (1992); *b*) K. Sato, T. Kusumoto, M. Kuroboshi, A. Nakayama, T. Hiyama, S. Takehara, M. Osawa, and K. Nakamura, Abstracts of Papers, 63rd National Meeting of the Chemical Society of Japan, Osaka, March 1992, No. 1F438.
2) *a*) H. E. Simmons, T. L. Cairns, S. A. Vladuchick, and C. M. Hoiness, *Org. React.*, **20**, 1 (1973); *b*) J. Furukawa, N. Kawabata, and J. Nishimura, *Tetrahedron*, **24**, 53 (1968).
3) *a*) C. D. Poulter, E. C. Friedrich, and S. Winstein, *J. Am. Chem. Soc.*, **91**, 6892 (1969); *b*) S. E. Denmark, J. P. Edwards, and S. R. Wilson, *ibid.*, **113**, 723 (1991).
4) *a*) H. Machleidt and R. Wessendorf, *Justus Liebigs Ann. Chem.*, **674**, 1 (1964); *b*) A. Thenappan and D. J. Burton, *J. Org. Chem.*, **55**, 4639

(1990).
5) *a*) Y. Kobayashi, T. Taguchi, T. Morikawa, T. Takase, and H. Takanashi, *Tetrahedron Lett.*, **21**, 1047 (1980); *b*) Y. Kobayashi, T. Morikawa, A. Yoshizawa, and T. Taguchi, *ibid.*, **22**, 5297 (1981); *c*) Y. Kobayashi, T. Taguchi, T. Morikawa, T. Takase, and H. Takanashi, *J. Org. Chem.*, **47**, 3232 (1982); *d*) Y. Kobayashi, T. Morikawa, and T. Taguchi, *Chem. Pharm. Bull.*, **31**, 2616 (1983); *e*) T. Morikawa, M. Uejima, and Y. Kobayashi, *Chem. Lett.*, **1988**, 1407; *f*) T. Morikawa, M. Uejima, K. Yoda, and T. Taguchi, *ibid.*, **1990**, 467.
6) The mixture of acetal derivatives contained $CyCH_2OCH_2OCH_2CH_3$ (Cy = fluorocyclopropane), $(CyCH_2O)_2CH_2$, and others (not determined), which were hydrolyzed to the parent alcohol derivative (**2a** or **2b**).
7) For recent examples of asymmetric Simmons–Smith reactions, see: *a*) A. Mori, I. Arai, and H. Yamamoto, *Tetrahedron*, **42**, 6447 (1986); *b*) E. A. Mash and D. S. Torok, *J. Org. Chem.*, **54**, 250 (1989); *c*); T. Imai, H. Mineta, and S. Nishida, *ibid.*, **55**, 4986 (1990); *d*) T. Sugimura, M. Yoshikawa, T. Futagawa, and A. Tai, *Tetrahedron*, **46**, 5955 (1990); *e*) M. P. Frutos, M. D. Fernandez, E. F.-Alvarez, and M. Bernabe, *Tetrahedron Lett.*, **32**, 541 (1991); *f*) A. B. Charette, B. Cote, and J.-F. Marcoux, *J. Am. Chem. Soc.*, **113**, 8166 (1991); *g*) Y. Ukaji, M. Nishimura, and T. Fujisawa, *Chem. Lett.*, **1992**, 61.
8) During the course of the present work, a related asymmetric Simmons–Smith reaction was utilized in the total synthesis of (+)-bicyclohumulenone (Y. Fukuyama, M. Hirono, and M. Kodama, *Chem. Lett.*, **1992**, 167). It is noteworthy that the opposite asymmetric induction (π-facial selectivity) related to the chiral center was observed in **14** in contrast with our case (**12**).

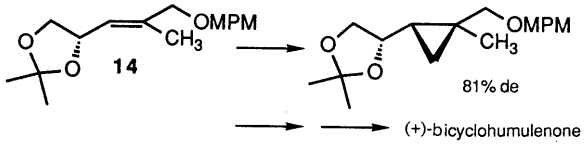


Chart 4