RADICAL CYCLIZATIONS TO FLUOROOLEFINS

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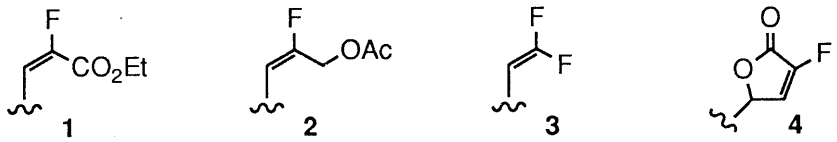
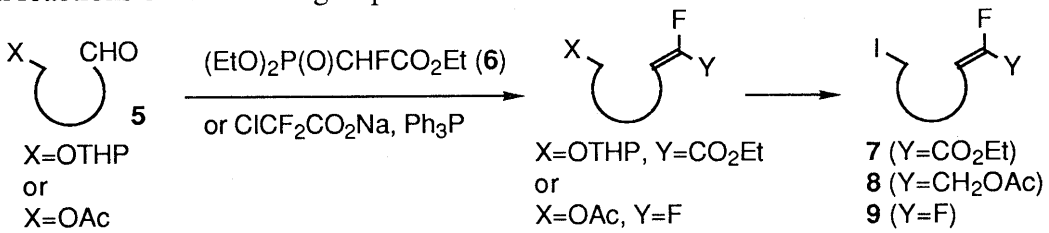
Radical cyclizations were effectively applied to systems containing fluoroolefins (α-fluoro-α,β-unsaturated ester, fluoroallyl acetate, *gem*-difluoroolefin, and fluorine-substituted unsaturated lactone) for the synthesis of ring compounds containing fluorine-substituted groups.

KEYWORDS radical cyclization; fluoroolefin; fluorine-containing ring compound; high dilution method; bicyclolactone; Corey lactone

Radical cyclizations are of considerable interest due to their synthetic potential for ring formation.[1] Specific chemoselectivity under free-radical conditions renders them applicable to substrates containing various functionalities. The stability of the C-F bond under the conditions of the tin hydride method has made it possible to investigate the radical cyclization of fluorine-substituted systems.[2] Fluoroolefin derivatives, easily prepared by Wittig type reactions, are building blocks commonly used in organofluorine chemistry. However, their applications to radical cyclization have not been well documented.[2a] This paper describes radical cyclizations involving fluoroolefins [α-fluoro-α,β-unsaturated ester (**1**), fluoroallyl acetate (**2**), *gem*-difluoroolefin (**3**), and fluorine-substituted unsaturated lactone (**4**)] as a radical acceptor.

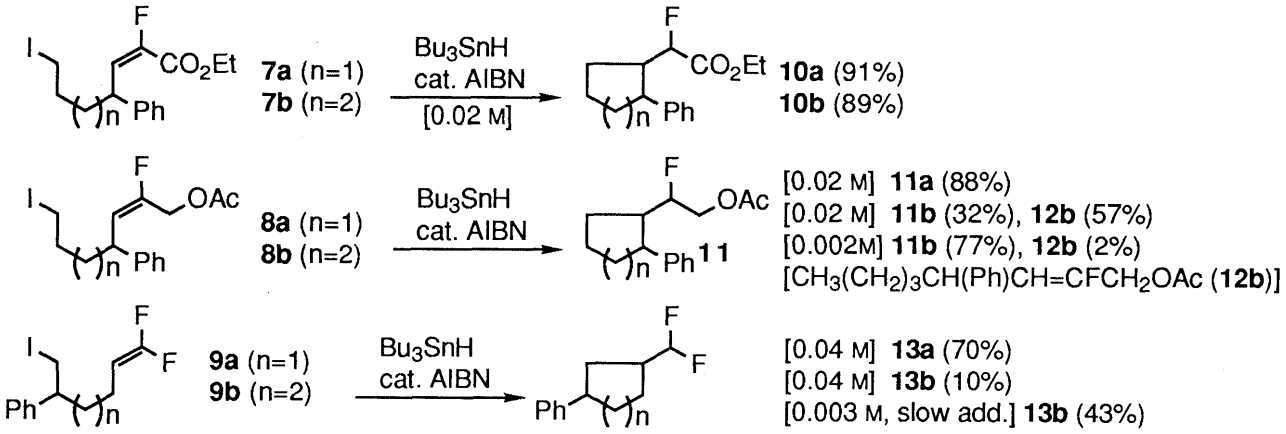


The substrates (**7**-**9**) containing fluoroolefin moieties (**1**-**3**) were prepared by Wittig ($Ph_3P{=}CF_2$)[3] or Emmons reactions [$(EtO)_2P(O)CHFCO_2Et$ (**6**)][4] with aldehyde derivatives (**5**) and the subsequent transformation reactions of functional groups.



Radical cyclization of the substrates (**7**, **8**, and **9**) was carried out by 1.2 eq of Bu_3SnH and a catalytic amount of AIBN in benzene at reflux temperature for 3 - 5 h.[5] Reactions of unsaturated ester derivatives (**7a**

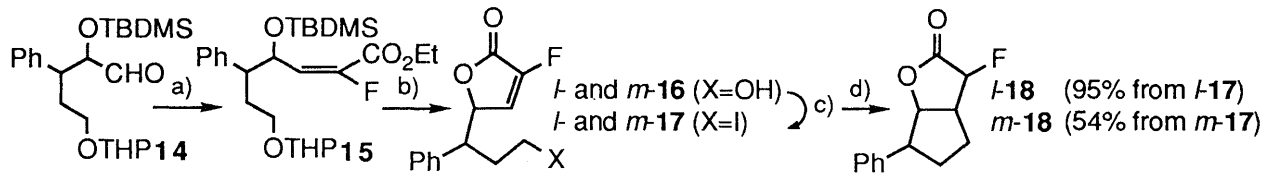
and **7b**) in a 0.02 M solution of Bu_3SnH gave the cyclopentane and cyclohexane derivatives (**10a**[6] and **10b**) via selective exo cyclization in 91% and 89% yields, respectively. Similarly, the allyl acetate derivative (**8a**) under the 0.02 M conditions gave a high yield (88%) of cyclopentane derivative (**11a**) via 5-exo cyclization.



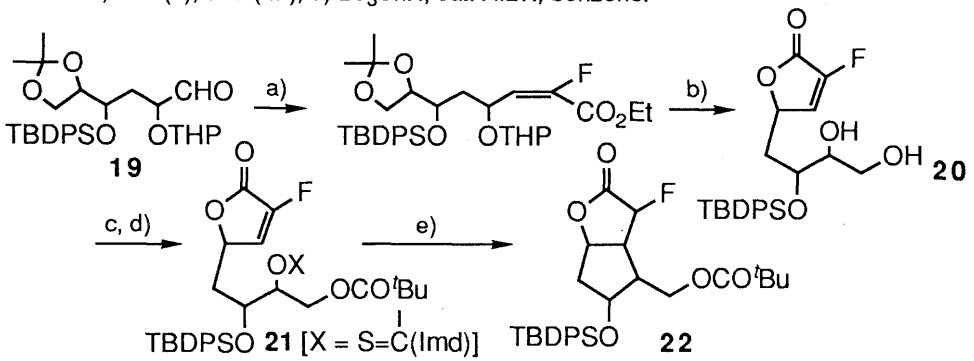
On the other hand, 6-exo cyclization of **8b** afforded a 32% yield of **11b** under the same conditions (0.02 M) along with the reduction product (**12b**) in 57% yield. The high dilution method for the cyclization of **8b** significantly improved the yield of **11b** by suppressing the reduction of the initial carbon radical with Bu_3SnH.[7] Thus, lowering the concentration of Bu_3SnH to 0.002 M (slow addition of Bu_3SnH by the syringe pump technique), the formation of **12b** was reduced (2%) and **11b** was obtained in 77% yield. Radical cyclizations to *gem*-difluoroolefin derivatives (**9a** and **9b**) also proceeded regioselectively in the exo mode to give **13a** and **13b**, respectively. Here, again, the high dilution method slightly improved the yield of 6-exo cyclization of **9b**.

Subsequently, the radical cyclization to α-fluoro-α,β-unsaturated lactone (**4**) was examined. Since the Emmons reaction of **6** exhibited the high E-selectivity (cis-relationship with respect to F and H), the cyclization system was easily prepared from the α-hydroxyaldehyde derivative (**14**). Deprotection-lactonization by treating **15** with *p*-TsOH in toluene-ethanol formed **16** as a diastereoisomeric mixture, which was then separated into less-polar and more-polar isomers (*l*- and *m*-**16**). Iodides (*l*- and *m*-**17**) derived from *l*- and *m*-**16** were subjected to radical cyclization, respectively. Reactions of *l*-**17** and *m*-**17** with Bu_3SnH gave bicyclolactones possessing the α-fluorine-substituent [*l*-**18** (95% yield) and *m*-**18** (54% yield), respectively].[8] By this approach to construct the bicyclolactone skeleton, a model study for the synthesis of fluorine-substituted Corey lactone was carried out. Retrosynthetically, the Corey lactone can be related back to the aldehyde derivative (**19**). The stereoselective Emmons reaction of **19** followed by deprotection of the acetal groups under acidic conditions gave the lactone (**20**). For cyclization via radical deoxygenation of the secondary hydroxyl group, **20** was converted to thiocarbonylimidazolide (**21**)[9] through pivaloylation. Tin hydride promoted the radical cyclization of **21** to give the bicyclolactone (**22**) in 43% yield as a stereoisomeric mixture,[10] which was a compound related to Corey lactone having α-fluorine substitution.

The present results clearly demonstrate the synthetic potential of fluoroolefins as radical acceptors in cyclization reactions. Fluoroolefination and radical cyclization conducted in conjunction is one means for synthesizing fluorine-containing ring compounds.



a) **6**, $NaN(SiMe_3)_2$/THF, 75%, b) *p*-TsOH/toluene-EtOH, 44%(*l*-) and 53%(*m*-), c) MsCl, Et_3N/CH_2Cl_2, then NaI/acetone, 91%(*l*-), 81%(*m*-), d) Bu_3SnH, cat. AIBN, benzene.



a) **6**, $NaN(SiMe_3)_2$/THF, 90%, b) HCl/toluene-EtOH, 55%, c) ^{t}BuCOCl/pyridine, 63%, d) $S=C(Imd)_2$/THF, 60%, e) Bu_3SnH, cat. AIBN, benzene, 43%.

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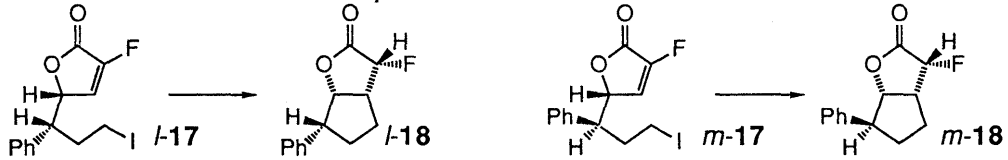
5) A mixture of two stereoisomers was obtained in each case except for **13a**; **10a** (2.9 : 1), **10b** (7.4 : 1), **11a** (1.3 : 1 by GLC), **11b** (1.6 : 1 in 0.02 M), **11b** (1.5 : 1 in 0.002 M), **13b** (2.2 : 1 in 0.04 M), **13b** (2 : 1 by GLC in 0.003 M). Cyclohexane derivatives (**10b** and **11b**) were trans isomers with respect to substituents on the ring. These were epimeric mixtures at the fluorine-substituted carbon atom.

6) Spectral data of the more polar isomer of **10a** (68%) as follows; ^{1}H-NMR δ: 1.03 (3H, t, J=7.2 Hz), 1.66-1.91 (4H, m), 2.00-2.19 (2H, m), 2.58-2.72 (1H, m), 3.08-3.15 (1H, m), 3.67 (1H, dq, J=10.8 and 7.2 Hz), 3.84 (1H, dq, J=10.8 and 7.2 Hz), 4.88 (1H, dd, J=48.8 and 3.5 Hz), 7.13-7.28 (5H, m). ^{19}F-NMR δ (from benzotrifluoride): -137.08 (dd, J=48.8 and 29.8 Hz). IR (neat): 1760 and 1739 cm^{-1}. High-resolution MS *m/z*: Calcd for $C_{15}H_{19}FO_2$: 250.1368. Found: 250.1375.

7) Compared with the cases of **8b** and **9b**, a high yield of the 6-exo cyclization of **7b** without high dilution conditions can be rationalized by preferencial attack of the nucleophilic alkyl radical to the electron-deficient olefin (α,β-unsaturated ester).

8) Ratio of stereoisomers; *l*-**18** (10 : 1), *m*-**18** (4.2 : 1). The major stereoisomers of *l*- and *m*-**18** were assigned based on the data of NOE experiments as shown below.



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10) In the present model study, stereochemical control is not discussed. Although (*R*)-glyceraldehyde-1,2-acetonide was used as the starting material for the synthesis of **19**, diastereomer separation for obtaining the single stereoisomer in chain-extension steps was difficult. **21** was a mixture of two diastereoisomers (2.3 : 1 by ^{1}H-NMR). The stereochemistry of **22**, a mixture of four stereoisomers (2.5 : 2 : 1.9 : 1), thus has yet to be fully clearified.

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