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Radical Induced Regio- and Stereoselective Ring-Opening of gem-Difluorocyclopropanes. Synthesis of the (E)-Difluoroallylic System

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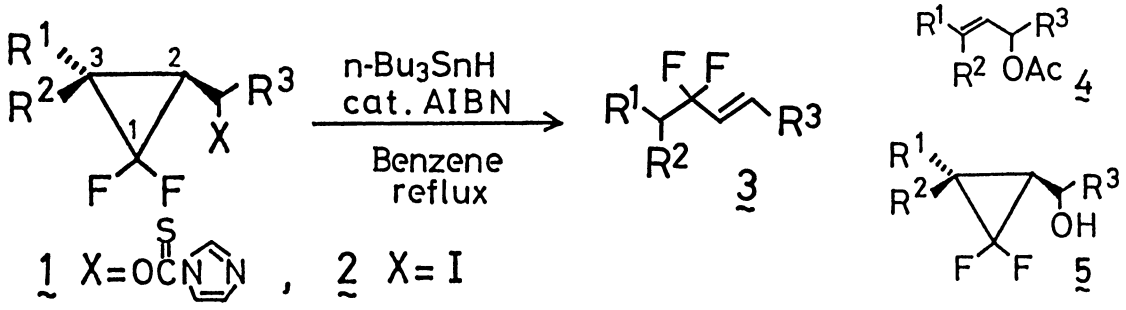
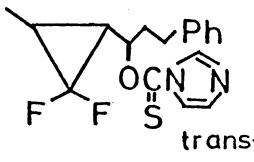
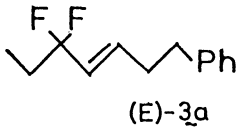
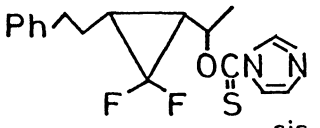
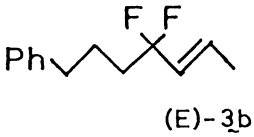
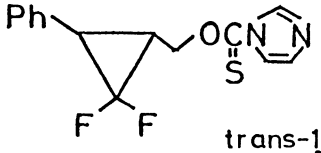
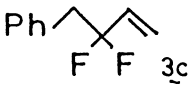
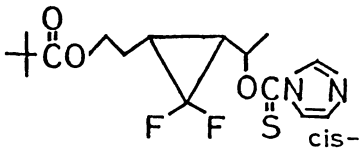
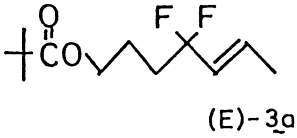
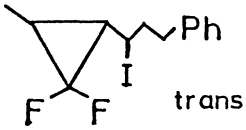
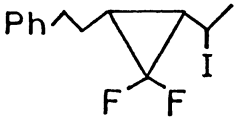
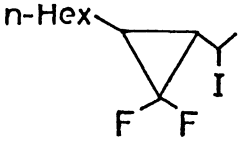
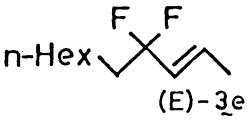
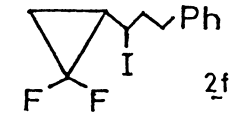
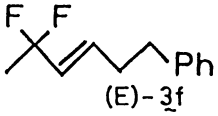
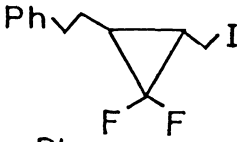
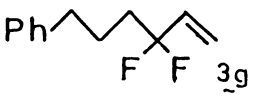
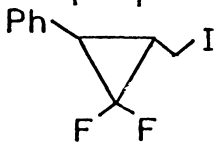
The radical induced regioselective ring-opening of gem-difluorocyclopropanes via deoxygenation or deiodination gave (E)-difluoroallylic compounds stereoselectively.

The free-radical mediated carbon-framework transformation is increasingly being used in organic synthesis, and highly regio-, stereo- and chemoselective radical processes are of current interest.[1] It is known that cyclopropylmethyl radicals undergo β-C-C bond cleavage to afford 3-butenyl radicals.[2] The regioselectivity of their ring-openings depends on the substituent on the cyclopropane ring and reaction conditions (kinetic control vs. thermodynamic control).[3] An E/Z-stereoisomeric mixture of the product is formed in relatively low selectivity when the substituent is present at the radical center formed initially.[4] As part of a program directed at the ring-opening reactions of gem-difluorocyclopropanes,[5] we made a detailed examination of their ring-opening under free-radical conditions, aiming to disclose the regio- and stereoselectivity of the ring-opening. To date, there has been only reported ring-opening of the most simple case, in which the reaction of 1,1-difluoro-2-(bromomethyl)cyclopropane with tributyltin hydride (n-Bu_3SnH) gave 3,3-difluoro-1-butene, exclusively.[6] The present paper reports the stereoselective synthesis of the (E)-difluoroallylic system via radical promoted regioselective ring-opening of gem-difluorocyclopropane derivatives (1 or 2).



We chose O-thiocarbonylimidazolide derivatives (1) and iodides (2) as starting materials for our radical mediated ring-opening. Difluorocyclopropylmethanols (5) was prepared from the corresponding allyl acetates (4) by the addition of difluorocarbene ($ClCF_2COONa$, 170 °C) followed by alkaline hydrolysis.[7] According to Barton's procedure,[8] O-thiocarbonylimidazolides (1) were obtained in good yields

Table 1. The Reaction of Difluorocyclopropanes (1 and 2) with n-Bu_3SnH

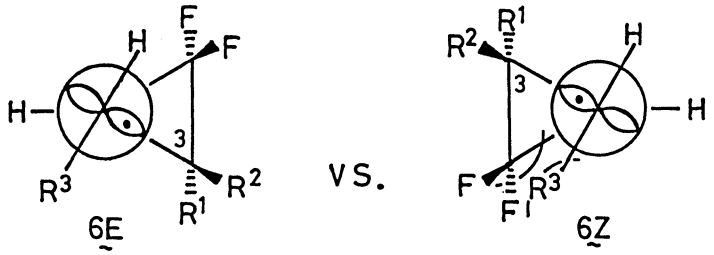
Entry	Difluorocyclopropane	Product	Yield/%
1	 trans-1a	 (E)-3a	83
2	 cis-1b	 (E)-3b	77
3	 trans-1c	 3c	45
4	 cis-1d	 (E)-3a	62
5	 trans-2a	(E)-3a	83
6	 a) cis-2b	(E)-3b	74
7	 trans-2e	 (E)-3e	62
8	 2f	 (E)-3f	69
9	 trans-2g	 3g	89
10	 trans-2c	3c	63

a) cis : trans = 83 : 17.

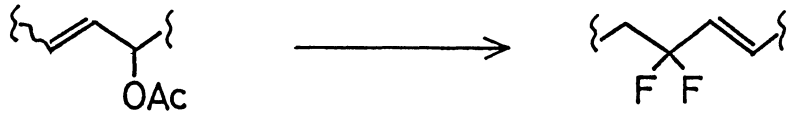
(73% - 95%) on treating 5 with 1,1'-thiocarbonyldiimidazole. The iodination of mesylates of 5 afforded iodides (2).[9]

When trans-difluorocyclopropane (1a) was reacted with n-Bu_3SnH (1.1 equiv.) in the presence of a catalytic amount of azobisisobutyronitrile (AIBN, 0.1 equiv.) in benzene at reflux temperature for 4 h, only (E)-3,3-difluoro-7-phenyl-4-heptene (3a) was obtained in 83% yield.[10] Under the same conditions, cis-cyclopropane (1b) underwent selective ring-opening to give (E)-3b in 77% yield.[11] Similar regio- and stereoselective ring-opening was also observed in the reaction of iodides (2) as the substrates. Both trand-2a and cis-2b provided good yields of (E)-difluoroallylic compounds (3a and 3b, respectively). The results are shown in Table 1. No regio- or stereoisomer was detected in any case.

In contrast to the regiochemical complexity in the ring-opening of non-fluorinated cis- and trans-cyclopropanes,[3] a CF_2 group shows the remarkable effect on the regioselectivity of homolytic cleavage of substituted gem-difluorocyclopropanes (C_2-C_3 scission). Neither substitution on C_3 by an alkyl or aryl group nor the stereochemical relationship of the substituents between C_2 and C_3 affected the regioselectivity of ring-openings of 1 and 2.



The high (E)-stereoselectivity observed here can be rationalized by a consideration of the favored transition state 6E: steric repulsion of R^3 with the cyclopropane ring disfavors the transition state 6Z. Since the stereochemical relationship of the substituents on C_2 and C_3 has no effect on the stereoselectivity of ring-opening, it is not likely that steric interactions between $R^2(R^1)$ and R^3 would contribute to transition state conformation.



In conclusion, a significant preference for ring-opening (C_2-C_3 scission) and the steric demands of the cyclopropane ring in the transition state permit this radical process to give the (E)-difluoroallylic system. Fluorine substitutions for hydrogens have been used to improve the biological activity of organic compounds in medicinal chemistry.[12] Use of this radical induced ring-opening provides one means for the stereoselective introduction of fluorine substitutions to the allylic position, starting from allyl acetate with homologation and migration of the double bond.

References

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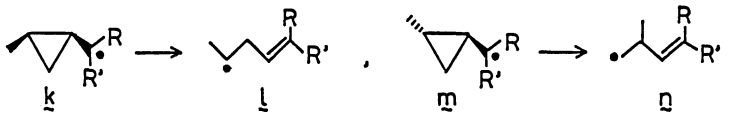
2) P. de Mayo, Rearrangements in Ground and Excited States, 1, 227 (1980).
3) For example, in the ring-opening reaction of 2-alkyl-substituted cyclopropylmethyl radicals cis-isomers (k) give thermodynamically favored secondary alkyl radical (l). On the other hand, their trans-isomers (m) give the primary alkyl radical (n) under conditions of kinetic control; when conditions of thermodynamic control are employed, the formation of secondary alkyl radical predominates; see P. M. Blum, A. G. Davies, M. Pereyre, and M. Patier, J. Chem.



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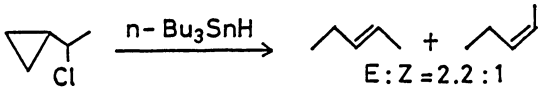
4) For example,



see Ref. 2, p.230 and reaction examples in Ref. 3.
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8) D. H. R. Barton, R. S. H. Motherwell, and W. B. Motherwell, J. Chem. Soc., Perkin Trans. 1, 1981, 2363 and references cited therein.
9) The yields of 2 from corresponding 5 are 34%-91%. The low yield (16%) of cis-2b is probably due to the steric congestion between R^2 and R^3.
10) (E)-3a: ^{1}H NMR ($CDCl_3$) δ=0.94 (3H, t, J=7.5 Hz), 1.87 (2H, tq, J=15.6 and 7.5 Hz), 2.42 (2H, m), 2.73 (2H, t, J=7.74 Hz), 5.54 (1H, dtt, J=15.76, 10.9, and 1.4 Hz), 6.08 (1H, dtt, J=15.76, 6.75, and 2.6 Hz), 7.16-7.30 (5H, m); ^{19}F NMR ($CDCl_3$, benzotrifluoride as an internal standard) δ=-34.8 (2F, td, J=15.6 and 10.9 Hz); IR (CCl_4) 3040, 2990, 2945, 1675, 1600, 1495 cm^{-1}; MS m/z 210 (M^+).
11) (E)-3b: ^{1}H NMR ($CDCl_3$) δ=1.75 (3H, dtd, J=6.67, 3.32, and 1.71 Hz), 1.78-1.96 (4H, m), 2.65 (2H, t, J=7.47 Hz), 5.54 (1H, dtq, J=15.65, 11.0, and 1.71 Hz), 6.04 (1H, dqt, J=15.65, 6.67, and 2.72 Hz), 7.16-7.30 (5H, m); ^{19}F NMR ($CDCl_3$) δ=-32.0 (2F, m); IR (CCl_4) 3040, 2960, 2930, 1680, 1455 cm^{-1}; MS m/z 210 (M^+).
12) R. Filler and Y. Kobayashi, Biomedicinal Aspects of Fluorine Chemistry, Kodansha Ltd. (Tokyo), Elsevier Biomedical Press (1982).

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