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Unusual Reaction Behavior of *gem*-Difluorocyclopropane Derivatives: Stereoselective Synthesis of β-Monofluoroallylic Alcohols, Ethers, Esters, and Amide

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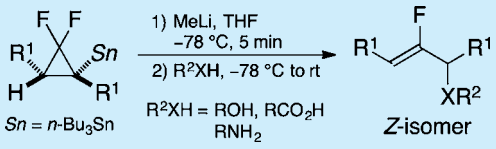
Supporting Information

ABSTRACT: On treating *gem*-difluorocyclopropylstannanes, derived from the radical hydrostannation of *gem*-difluorocyclopropenes, with 1.5 equiv of MeLi in THF at −78 °C for 5 min, followed by quenching the reaction with various agents, such as H_2O, alcohols, carboxylic acids, and tosylamide, the corresponding β-fluoroallylic alcohols, ethers, esters, and amide were obtained with exclusive *Z*-selectivity in acceptable yields.



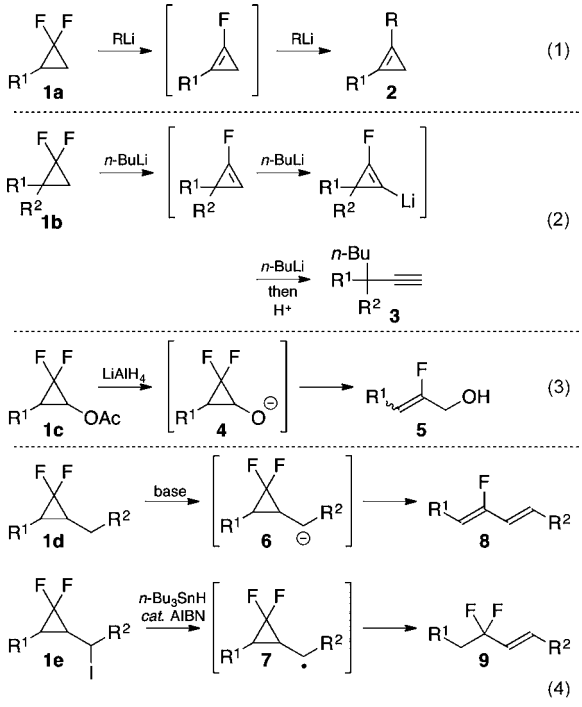
gem-Difluorocyclopropane derivatives have been attracting much interest in the fields of materials, medicinal, and pharmaceutical sciences due to their unique characteristics and biological activities exerted by a fluorine atom.[1] At the same time, they have also been recognized as one of the most valuable building blocks in synthetic organic chemistry because they can be easily transformed into structurally different types of organic molecules. For example, treatment of 2-monosubstituted 1,1-difluorocyclopropane **1a** with 2.0 equiv of organolithium reagents RLi, such as *n*-BuLi, MeLi, and PhLi, in THF at −70 °C gives the corresponding disubstituted cyclopropenes **2** in high yields via dehydrofluorination and the subsequent addition−elimination of organolithium reagents toward the monofluorocyclopropene (Scheme 1 eq 1).[2] On the other hand, 2,2-disubstituted 1,1-difluorocyclopropanes **1b** react with 3.0 equiv of *n*-BuLi to afford the corresponding alkynes **3** via dehydrofluorination and the subsequent ring-opening reaction (Scheme 1 eq 2).[2] In addition, 2-acetoxy-1,1-difluorocyclopropanes **1c** react with $LiAlH_4$ to provide the corresponding *gem*-difluorocyclopropoxides **4**, which undergo the ring-opening reaction and the subsequent reduction, giving rise to the β-fluoroallylic alcohols **5** (Scheme 1 eq 3).[3] *gem*-Difluorocyclopropylmethyl anions **6** or radicals **7**, generated from **1d** or **1e**, also undergo the ring-opening reaction to give the corresponding monofluorinated dienes **8** or difluorinated compounds **9**, respectively (Scheme 1 eq 4).[4]

In this way, *gem*-difluorocyclopropane derivatives are significantly important synthetic intermediates from the viewpoint of synthesizing various types of organic molecules, and research on the development of their synthetic methods and their synthetic applications is now under investigation.[5]

Here, we report preliminary findings on a first unique ring-opening reaction of *gem*-difluorocyclopropylstannanes, providing β-fluoroallylic alcohols, ethers, esters, and an amide in an exclusively *Z*-selective manner.

Initial studies began with the preparation of *gem*-difluorocyclopropylstannanes, as shown in Scheme 2. Thus, treatment

Scheme 1. Precedent Synthetic Applications of Difluorocyclopropanes



of **10a** (R = Ph)[6] with 1.2 equiv of n-Bu_3SnH in the presence of 20 mol % of Et_3B in toluene at 80 °C for 4 h gave (1*R**,3*S**)-tributyl-(2,2-difluoro-1,3-diphenylcycloprop-1-yl) stannane **11a** quantitatively. In this case, the product was obtained in an exclusively *trans*-selective addition manner, and no other stereoisomer could be detected at all.[7,8] Even when

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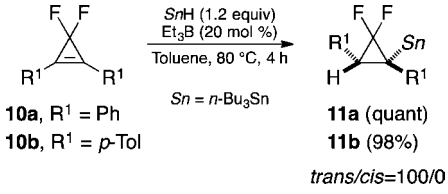
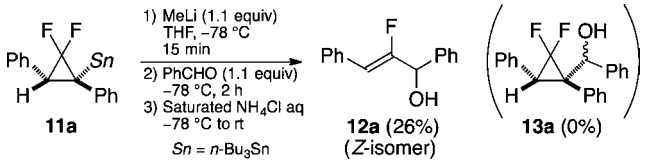
Scheme 2. Preparation of *gem*-Difluorocyclopropylstannanes 11



10b was used instead of **10a**, the *trans*-addition product **11b** was obtained in 98% yield as a single isomer.

As a synthetic application of *gem*-difluorocyclopropylstannanes, the coupling reaction of thus obtained **11a** with benzaldehyde was examined (Scheme 3). Thus, **11a** was

Scheme 3. Ring-Opening Reaction of *gem*-Difluorocyclopropane Derivative 11a

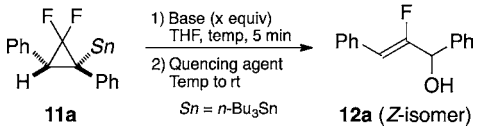


subjected to MeLi in THF at −78 °C for 15 min, followed by the addition of 1.1 equiv of benzaldehyde into the reaction mixture. After the mixture was stirred at that temperature for 2 h, the reaction was quenched with saturated NH_4Cl aqueous solution. Very surprisingly, β-fluoroallylic alcohol **12a** with exclusive *Z*-stereoselectivity was produced in 26% yield.[9] In this case, **12a** was the only fluorine-containing product, and the expected coupling adduct **13a** could not be detected at all. It was revealed that the Barbier type reaction[10] was not effective in providing **13a**, and in this case **12a** was also afforded in 10% yield as a single isomer (not shown in Scheme 3).

For this unique ring-opening reaction, we next investigated the reaction conditions to improve the yield of **12a**. The results are summarized in Table 1.

Thus, treatment of **11a** with MeLi (1.1 equiv) in THF at −78 °C for 5 min without benzaldehyde, followed by

Table 1. Investigation of the Reaction Conditions



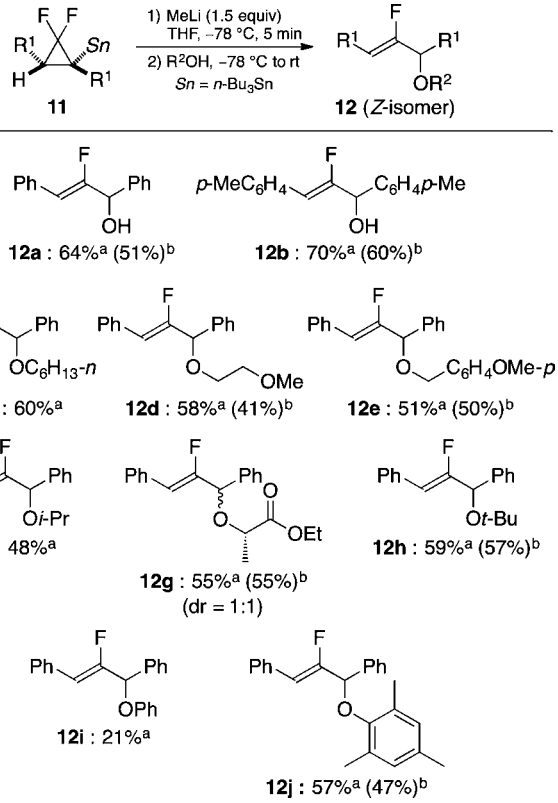
entry	base	*x*/ equiv	temp/ °C	quenching agent	yield[a]/ % of **12a**	recovery[a] / % of **11a**
1	MeLi	1.1	−78	NH_4Cl aq	28	22
2[b]	MeLi	1.1	−78	NH_4Cl aq	31	15
3	BuLi	1.1	−78	NH_4Cl aq	0	63
4[c]	MeLi	1.1	−78	NH_4Cl aq	0	quant
5	MeLi	1.5	−78	NH_4Cl aq	51	0
6	MeLi	1.5	−78	H_2O	51	0
7	MeLi	1.5	−78	3% HCl aq	64 (51)	0
8	MeLi	1.5	−60	3% HCl aq	52	0
9	MeLi	1.5	0	3% HCl aq	29	23

[a]Determined by ^{19}F NMR. Value in parentheses is of isolated yield. [b]HMPA (1.0 equiv) was used. [c]Et_2O was used instead of THF.

quenching the reaction with a saturated NH_4Cl aqueous solution, gave the corresponding β-fluoroallylic alcohol **12a** in 28% yield. In this case, 22% of the starting material **11a** still remained unreacted (Table 1, entry 1). The addition of HMPA did not bring about any dramatic change in the yield (Table 1, entry 2). The reaction did not proceed smoothly with *n*-BuLi or in Et_2O (Table 1, entries 3, 4). The yield of **12a** was greatly enhanced when the amount of MeLi was increased from 1.1 to 1.5 equiv (Table 1, entry 5). H_2O was also effective in this ring-opening reaction (Table 1, entry 6), and in particular, a 3% HCl aqueous solution was found to be the quenching agent of choice, **12a** being obtained in 64% yield (Table 1, entry 7). A higher reaction temperature significantly decreased the yield (Table 1, entries 8, 9).

With the best reaction conditions in hand, the scope and limitation for the ring-opening reaction were examined as summarized in Schemes 4 and 5.

Scheme 4. Ring-Opening Reaction with Various R^2OH



[a]Yields are determined by ^{19}F NMR. [b] Values in parentheses are of isolated yield.

First, the alcohol **12b** was given in 70% yield in a highly stereoselective manner even when **11b**, having a tolyl group instead of a phenyl group as a substituent R^1, was employed. Various primary alcohols, such as *n*-hexyl alcohol, ethylene glycol monomethyl ether, and *p*-methoxybenzyl alcohol, could be successfully applied as a quenching agent for the ring-opening reaction, with the corresponding ethers **12c**, **12d**, and **12e** being obtained in 60%, 58%, and 51% yields, respectively. Secondary alcohols, such as isopropyl alcohol and (*S*)-ethyl lactate, were also found to be good substrates (**12f** and **12g**). Even with a much bulkier *tert*-butyl alcohol rather than primary and secondary alcohols, the corresponding ether **12h**

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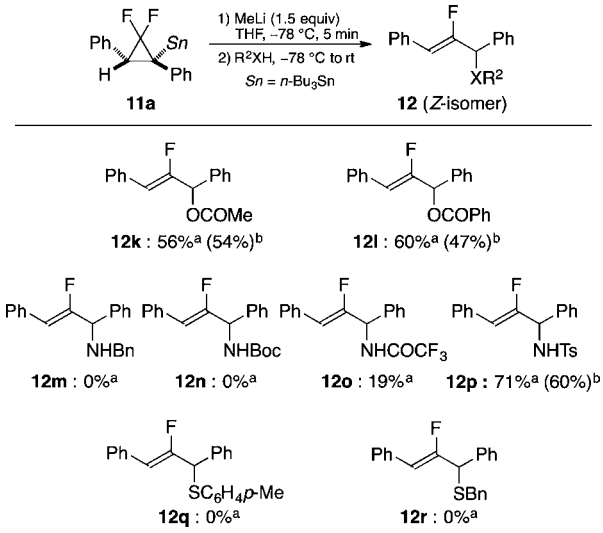
Scheme 5. Ring-Opening Reaction with Various Quenching Agents



[a]Yields are determined by ^{19}F NMR. [b] Values in parentheses are of isolated yield.

was provided in a comparable yield. Very interestingly, 2,4,6-trimethylphenol served well as a quenching agent in the reaction (**12j**) while the use of phenol caused a significant decrease in the yield (**12i**).

As shown in Scheme 5, we next examined all different types of quenching agents instead of alcohols or phenols. Various carboxylic acids, such as acetic acid or benzoic acid, gave the corresponding *β*-fluoroallyl acetate **12k** or benzoate **12l** in good yields. Very disappointingly, the desired allylamine **12m** or amide **12n** was not detected at all in the case of benzylamine or *tert*-butyl carbamate as a quenching agent. In addition, only 19% of *β*-fluoroallylamide **12o** was provided when trifluoroacetamide was used. In sharp contrast, quenching the reaction with *p*-toluenesulfonamide brought about the corresponding amide **12p** in a high yield. It was revealed that thiols, such as *p*-toluenethiol and benzylthiol, were not suitable for the ring-opening reaction.

On the basis of the fact that nonfluorinated cyclopropenes **13** and **14** were detected as byproducts in some cases (Figure 1),[11] and that quenching the reaction with D_2O gave the

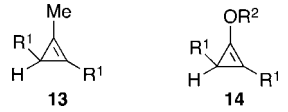
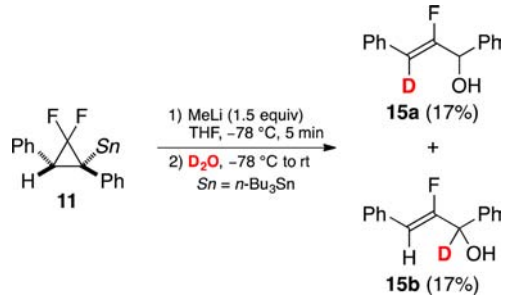


Figure 1. Byproducts.

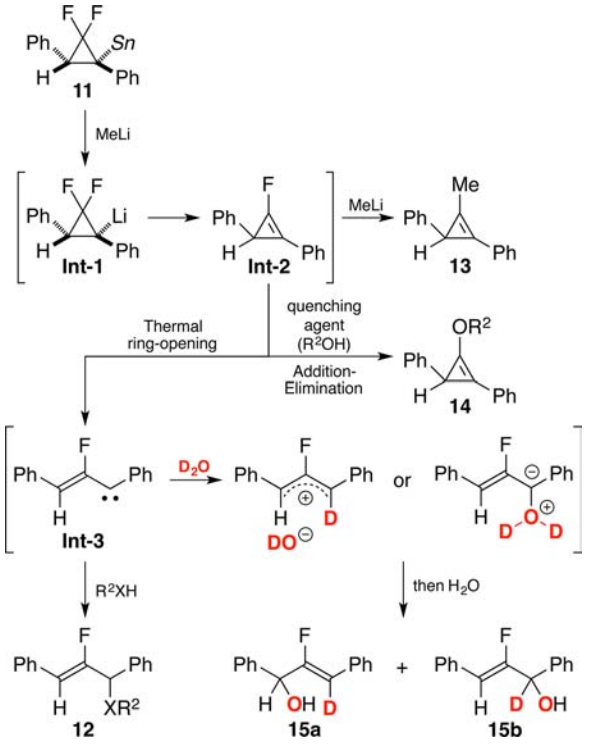
corresponding deuterated adducts **15a** and **15b** in a ratio of 1:1 (Scheme 6), a plausible reaction mechanism can be proposed as shown in Scheme 7.

First, the lithium–tin exchange reaction may take place to give the corresponding *gem*-difluorocyclopropyl lithium intermediate **Int-1**, which may undergo *β*-elimination to afford the monofluorocyclopropene **Int-2**. This monofluorocyclopropene can partially react with MeLi, leading to the corresponding nonfluorinated trisubstituted cyclopropenes **13** via the addition–elimination pathway. Quenching the reaction with alcohols (R^2OH) may partially cause the substitution of

Scheme 6. Reaction with D_2O as a Quenching Agent



Scheme 7. A Plausible Reaction Mechanism



R^2O^- toward **Int-2** via the addition–elimination pathway, providing the cyclopropenyl ether **14**. On the other hand, it is highly possible that **Int-2** mainly invokes a thermal ring-opening reaction to provide the corresponding carbene **Int-3** which is significantly stabilized by the resonance effect of an aromatic ring.[12] Finally, exposure of **Int-3** to a quenching agent (R^2XH) may lead to the corresponding *β*-fluoroallylic alcohols, ethers, and amide **12**. Given that the reaction may proceed through the carbene **Int-3**, it is obvious that quenching the reaction with D_2O results in a stereorandom formation of **15a** and **15b**.

In summary, we have discovered a unique ring-opening reaction of *gem*-difluorocyclopropylstannanes to provide *β*-fluoroallylic alcohols, ethers, and an amide in a highly *Z*-selective manner. In this reaction, it is noteworthy that a heteroatom-containing substituent can be introduced into the *β*-fluoroallylic framework at the point of quenching the reaction. Further efforts to clearly understand the reaction mechanism and explore the synthetic utility of the reaction are currently underway.

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■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(6) *gem*-Difluorocyclopropenes **10a** and **10b** were prepared according to the literature. See: Wang, F.; Luo, T.; Hu, J.; Wang, Y.; Krishnan, H. S.; Jog, P. V.; Ganesh, S. K.; Prakash, G. K. S.; Plah, G. A. *Angew. Chem., Int. Ed.* **2011**, *50*, 7153−7157.

(7) The stereochemistry was determined based on the hydrostannation of the fluoroalkylated alkynes. See ref 8.

(8) Our research group has reported that the Et_3B-initiated hydrostannation reaction of fluoroalkylated alkynes proceeded in a highly *trans*-selective manner. See: (a) Konno, T.; Kishi, M.; Ishihara, T.; Yamada, S. *Tetrahedron* **2014**, *70*, 2455−2463. (b) Konno, T.; Morigaki, A.; Ninomiya, K.; Miyabe, T.; Ishihara, T. *Synthesis* **2008**, 564−572. (c) Chae, J.; Konno, T.; Kanda, M.; Ishihara, T.; Yamanaka, H. *J. Fluorine Chem.* **2003**, *120*, 185−193.

(9) The stereochemistry of the *β*-fluoroallylic alcohol was determined based on the coupling constant of *trans* H−F. For details, see Supporting Information.

(10) The reaction was carried out by the addition of MeLi etherial solution into the THF mixture of **10a** and benzaldehyde.

(11) In addition to **13** and **14**, a very small amount of (*Z*)-2-fluoro-1,3-diphenyl-1-propene was also obtained.

(12) It has been well-known that a ring-opening reaction of cyclopropene could take place even under low temperature to afford the corresponding vinyl carbene. See: (a) Baird, M. S. *Chem. Rev.* **2003**, *103*, 1271−1294. (b) Weber, J.; Brinker, U. H. *Tetrahedron* **1996**, *52*, 14641−14650. (c) Al Dulayymi, J. R.; Baird, M. S. *Tetrahedron Lett.* **1995**, *36*, 3393−3396. (d) Al Dulayymi, A. R.; Al Dulayymi, J. R.; Baird, M. S.; Rajaram, L. *Tetrahedron* **1995**, *51*, 8371−8382. (e) Al Dulayymi, J. R.; Baird, M. S.; Fitton, H. L.; Rajaram, L. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1633−1641. (f) Al Dulayymi, J. R.; Baird, M. S.; Fitton, H. L. *Tetrahedron Lett.* **1992**, *33*, 4803−4806. (g) Al Dulayymi, J. R.; Baird, M. S. *Tetrahedron* **1989**, *45*, 7601−7614. (h) Baird, M. S.; Hussain, H. H. *Tetrahedron* **1989**, *45*, 6221−6238. (i) Al Dulayymi, J.; Baird, M. S.; Hussain, H. H. *Tetrahedron Lett.* **1989**, *30*, 2009−2012. (j) Al Dulayymi, J. R.; Baird, M. S.; Clegg, W. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1799−1803. (k) Al Dulayymi, J.; Baird, M. S. *Tetrahedron Lett.* **1988**, *29*, 6147−6148. (l) Al Dulayymi, J.; Baird, M. S. *Tetrahedron Lett.* **1988**, *29*, 6149−6152. (m) Baird, M. S. *Tetrahedron Lett.* **1984**, *25*, 4829−4832. (n) Baird, M. S.; Buxton, S. R.; Whitley, J. S. *Tetrahedron Lett.* **1984**, *25*, 1509−1512.