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Synthesis of *gem*-Difluoromethylene Building Blocks through Regioselective Allylation of *gem*-Difluorocyclopropanes

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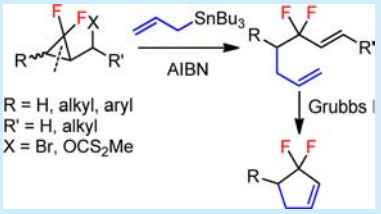
Supporting Information

ABSTRACT: *gem*-Difluorocyclopropane derivatives react with allyltributylstannane in the presence of 2,2′-azobis(isobutyronitrile) to afford 1,6-dienes with a *gem*-difluoromethylene moiety at the allylic position. The reaction proceeds regioselectively with high yields, and the 1,6-dinenes obtained are good precursors for cyclic systems containing a *gem*-difluoromethylene moiety. Although *S*-methyl carbonodithioate also works as a leaving group, rearrangement of the leaving group competes with the desired allylation, depending on the amount of allyltributylstannane.



The incorporation of a fluorine atom into an organic molecule can alter the chemical reactivity of the resulting compound due to the strong electron-withdrawing nature of fluorine, thus making it possible to create a new molecule that exhibits unique physical and biological properties.[1] As a result, much attention has focused on the preparation of *gem*-difluoromethylene derivatives as a source of novel functional materials.[1,2] Syntheses of such compounds have generally been achieved by difluorination of carbonyl or thiocarbonyl functional groups.[3] However, the number of fluorination reagents is limited and the reagents are generally very expensive; hence, synthetic strategies that use building blocks containing a *gem*-difluoromethylene moiety have been recognized as an attractive alternative route through which to access *gem*-difluoromethylene compounds. Over the years, we synthesized a range of *gem*-difluorocyclopropane derivatives and revealed their unique physical and biological properties; as a result of these studies, numerous types of *gem*-difluorocyclopropane compounds are now available.[2] Kobayashi and co-workers reported a radical-induced regioselective ring-opening reaction of [2,2-difluoro-3-(iodomethyl)cyclopropyl]benzene and succeeded in preparing (2,2-difluorobut-3-en-1-yl)benzene derivatives.[4] Dolbier and co-workers reported that radical-type cleavage of the *gem*-difluorocyclopropane ring took place very quickly.[5] More recently, Gurjar and co-workers reported the preparation of a diallyl-substituted compound through a ring-opening reaction of (halomethyl)cyclopropanes with allyltributylstannane ($allylBu_3Sn$).[6] Inspired by these works, we hypothesized that a novel *gem*-difluoromethylene compound **2** might be obtained from *gem*-difluorocyclopropane **1** through radical-type allylation following regioselective ring opening (Figure 1).

Here, we wish to report the preparation of *gem*-difluoromethylene compounds **2** by the radical-type ring-opening reaction of *gem*-difluorocyclopropane **1**. The *cis* isomer of 1-bromomethyl-2-benzyloxymethyl-3,3-difluorocyclopropane

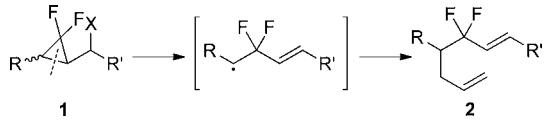
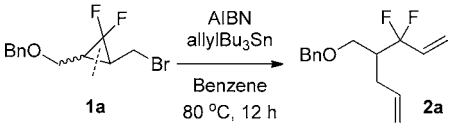


Figure 1. Working hypothesis of the present synthetic project.

(**1a**; R = $BnOCH_2$) was initially selected as the substrate for the present study because it was established that decomposition of the *cis* isomer of 1,2-dialkyl-3,3-difluorocyclopropane took place more easily than that of its *trans* isomer.[7]

The reaction was conducted as follows (Table 1): a mixture of **1a** (R = $BnOCH_2$),[8] $allylBu_3Sn$, and a catalytic amount of 2,2′-azobis(isobutyronitrile) (AIBN) in benzene (1.0 M) was

Table 1. Optimizations for Regioselective Allylation



entry	amount of $allylBu_3Sn$ (equiv)	amount of AIBN (%)	yield[a] (%)
1	2.0	3.6	5[b]
2	2.0	25	25
3	6.0	5	68
4	7.0	5	84
5	7.0	5	62[c]
6	8.0	5	89
7	10	5	71
8	8.0	5	89[d]

[a]Isolated yield. [b]NMR yield based on trioxane as an internal standard. [c]The reaction was carried out in toluene at 80 °C. [d]The *trans* isomer of **1a** was used.

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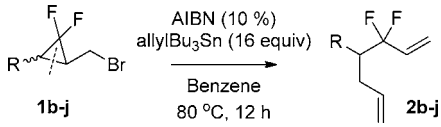
stirred at 80 °C for 12 h and then treated with a mixed solvent of ethyl acetate and a saturated aqueous potassium fluoride (KF) solution at room temperature for 1 h to initiate precipitation. The precipitate formed was removed by filtration, the filtrate was evaporated, and subsequent purification of the residue by silica gel thin-layer chromatography (TLC) afforded **2a** (R = $BnOCH_2$). By using various types of 1-alkyl-2-bromomethyl-3,3-difluorocyclopropane **1**, regioselective allylation under the above conditions gave a range of products, **2**; the results are summarized in Table 2.

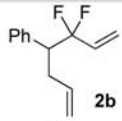
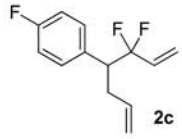
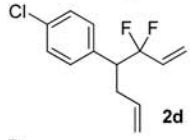
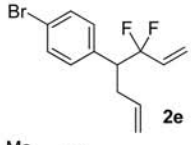
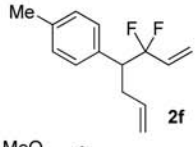
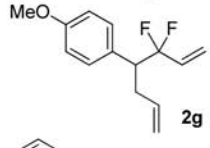
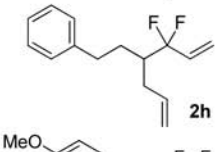
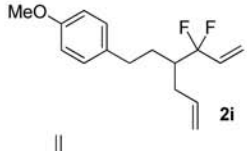
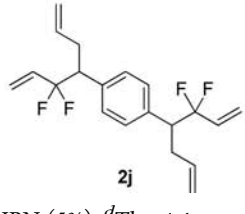
Initially, we conducted the reaction by using **1a** in the presence of 2.0 equiv of allylBu_3Sn and 3.6% AIBN. The desired product **2a** was, however, obtained in only poor yield under these conditions (Table 1, entry 1). Increasing the amount of allylBu_3Sn improved the chemical yield of the product significantly, and **2a** was obtained in 68%, 84%, and 89% yields when 6, 7, and 8 equiv of allylBu_3Sn were used, respectively (entries 3, 4, and 6). The yield dropped, however, when 10 equiv of allylBu_3Sn were employed in the reaction (entry 7). A slight drop of the chemical yield of **2a** was recorded when the reaction was carried out in toluene (entry 5). Although we initially expected that the *cis* isomer of *gem*-difluorocyclopropane would be more reactive than the *trans* isomer, no difference in the reactivity was observed, and the chemical yields of the products were similar (entries 6 and 8).

It was thus found that the amount of allylation reagent was important to achieve the desired reaction. In particular, a large excess of allylBu_3Sn was required for the reaction of [3-(bromomethyl)-2,2-difluorocyclopropyl]benzene (**1b**; R = Ph) because of the relatively poor reactivity of the radical generated by the ring-opening reaction. The desired product **2b** was obtained in 71% yield in the presence 16 equiv of allyBu_3Sn, whereas only a moderate yield (45%) was obtained when the reaction was carried out with 8 equiv of allylBu_3Sn (Table 2, entries 1 and 2). No difference was observed between the *trans* and *cis* isomers of **1b** (entries 2 and 3). The presence of electron-withdrawing substituents on the benzene ring, such as fluorine, chlorine, or bromine, contributed to an improved product yield, and the desired products **2c** (R = 4-F−C_6H_4), **2d** (R = 4-Cl−C_6H_4), and **2e** (R = 4-Br−C_6H_4) were obtained in 84%, 89%, and 84% yields, respectively (entries 4, 5, and 6). Conducting the reaction with 2-arylcyclopropanes substituted with an electron-donating group at the 4-position led to more complex results. Whereas **1f** (R = 4-Me−C_6H_4) gave the desired product **2f** in excellent yield (entry 7), **1g** (R = 4-MeO−C_6H_4) afforded **2g** in poor yield (25%) together with the formation of unidentified byproducts (entry 8). Reaction of *gem*-difluorocyclopropane derivatives with aliphatic substituents such as **1h** (R = $PhCH_2CH_2$) and **1i** (R = 4-MeO−C_6H_4−CH_2CH_2) proceeded very smoothly with 2 equiv of allylBu_3Sn and gave the products **2h** and **2i** in 77% and 68% yields, respectively (entries 9 and 10). Furthermore, the allylation was applicable to bis-*gem*-difluorocyclopropane **1j**, and the desired product **2j** was attained in 72% yield, although in this case the reaction required an excess of allylBu_3Sn to reach completion (entry 11).

Xanthate is known to be a good leaving group in the formation of a radical species,[9] so we next attempted allylation using xanthates **1k**, **1l**, and **1m**. The desired product **2h** was indeed obtained in 50% yield by using 2.0 equiv of allyl-Bu_3Sn with *O*-[(2,2-difluoro-3-phenethylcyclopropyl)-methyl] *S*-methyl carbonodithioate (**1k**). Compound **1l** was also attained in 70% yield as a mixture of *E*/*Z* isomers (83:17) when *O*-[1-(2,2-difluoro-3-phenethylcyclopropyl)-ethyl] *S*-methyl carbonodithioate (**1l**) was used as a substrate, although the reaction required 8.0 equiv of allylBu_3Sn (Figure 2). On the other hand, a mixture of two compounds, (*E*)-(5,5-difluoro-nona-3,8-dien-1-yl)benzene (**2m**) and (*E*)-*S*-(2,2-difluoro-6-phenylhex-3-en-1-yl) *S*-methyl carbonodithioate (**3**), was obtained when *O*-[1-(2,2-difluorocyclopropyl)-3-phenylpropyl]

Table 2. Scope of the Substrates



entry	R (substrate)	product	yield[a] (%)
1	Ph **1b**	 **2b**	45[b]
2	Ph **1b**	**2b**	71[c]
3	Ph **1b**	**2b**	72[d]
4	4-F-C_6H_4 **1c**	 **2c**	84
5	4-Cl-C_6H_4 **1d**	 **2d**	89
6	4-Br-C_6H_4 **1e**	 **2e**	84
7	4-Me-C_6H_4 **1f**	 **2f**	90
8	4-MeO-C_6H_4 **1g**	 **2g**	25
9	Ph-C_2H_4 **1h**	 **2h**	77[e]
10	4-MeO-C_6H_4-CH_2CH_2 **1i**	 **2i**	68[e]
11	4-BrCH_2($C_3H_2F_2$)-C_6H_4 **1j**	 **2j**	72

[a]Isolated yield. [b]AIBN (25%). [c]AIBN (5%). [d]The *cis* isomer of **1b** was used. [e]2 equiv of allylBu_3Sn were used.

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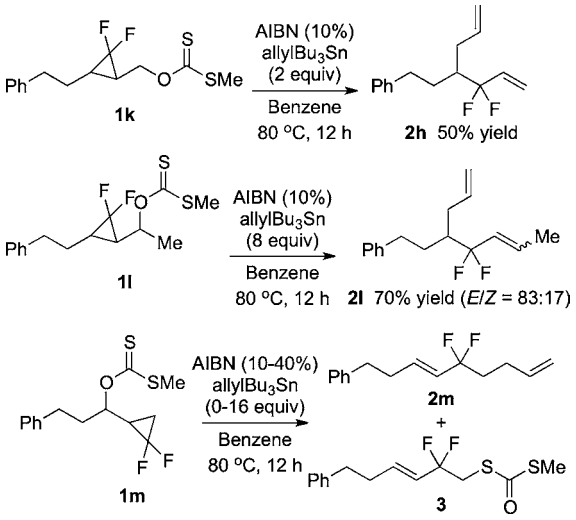


Figure 2. Allylation of *gem*-difluorocyclopropanes equipped with the *S*-methyl carbonodithioate as a leaving group.

S-methyl carbonodithioate (**1m**) was subjected to the reaction conditions (Figure 2).

Figure 3 shows a plausible mechanism of formation for the two products **2m** and **3**, starting from **1m**. Cyclopropane **1m**

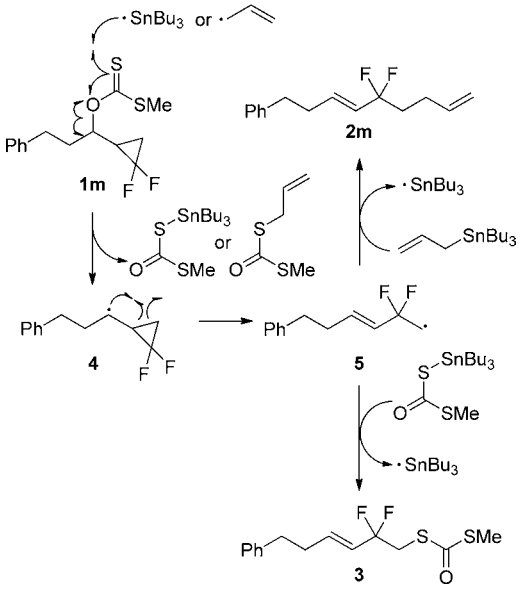


Figure 3. A plausible mechanism of formation of two products **2m** and **3** through ring opening of *gem*-difluorocyclopropane.

reacts with a tributylstannyl radical to give 2,2-difluorocyclopropylcarbinyl radical **4**. It has been reported that this radical species undergoes an extraordinarily fast ring-opening reaction.[5] Thus, a ring-opening reaction of radical **4** would take place to rapidly produce **5**, which would either be trapped by allylBu$_3$Sn to afford **2m** or generate the rearranged product **3** by trapping with *S*-methyl *S*-(tributylstannyl) carbonodithioate under low concentrations of allylBu$_3$Sn.

According to the proposed mechanism, we concluded that selective production might be possible by simply changing the amount of allylBu$_3$Sn (Table 3). As expected, it was found that **2m** was indeed obtained in 75% yield as the major product when a large excess of allylBu$_3$Sn (16 equiv) was employed in

Table 3. Results of Radical Type Allylation of *gem*-Difluorocyclopropane 1m

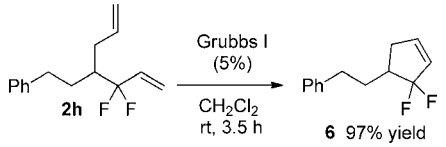
entry	allyBu$_3$Sn (equiv)	amount of AIBN (%)	yield of **2m** (%)	yield of **3** (%)
1	4.0	10	50[a]	35[a]
2	8.0	10	55[a]	22[a]
3	16	10	75[b]	15[b]
4	0	25	0	trace
5	1.0	25	25[b]	65[b]
6	0.5	40	15[b]	70[b]
7	0.5	40[c]	14[b]	74[b]

[a]NMR yield. [b]Isolated yield. [c]1,1′-Azobis(cyclohexanecarbonitrile) (V-40) was used as a radical initiator.

the presence of 10% AIBN (entry 3). On the other hand, compound **3** was obtained as the major product in 70% yield when the reaction was carried out using 0.5 equiv of allylBu$_3$Sn in the presence of 40% AIBN (entry 6). It has been reported that the rate of decomposition of the radical initiator is important to achieve the desired radical trapping.[10] In fact, a slight increase in the yield of **3** was recorded when 1,1′-azobis(cyclohexanecarbonitrile) (V-40) was used as the radical initiator (entry 7).

We then demonstrated a simple application of *gem*-difluoromethylene building block **2h** (Scheme 1). The ring-

Scheme 1. Preparation of (2-(2,2-Difluorocyclopent-3-en-1-yl)ethyl)benzene (6) Derived from 2h through the Ring-Closing Metathesis Reaction



closing metathesis reaction proceeded smoothly, and cyclopentene **6** was obtained in excellent yield (97%) when diene **2h** was treated with 5% Grubbs catalyst (first generation).[11]

In summary, we have accomplished the regioselective allylation of *gem*-difluorocyclopropane derivatives through a radical-type ring-opening reaction. Although the reaction requires a relatively large amount of allylBu$_3$Sn, unique *gem*-difluoromethylene compounds were produced. We have also demonstrated an application of one of the resultant *gem*-difluoromethylene compounds. Because *gem*-difluorocyclopropane is easily prepared from relatively inexpensive 2-chloro-2,2-difluoroacetic acid, the present method opens the way to an economical synthesis of useful *gem*-difluoromethylene compounds. Fluorine-containing molecules are now established as key compounds in medicinal and material chemistry. Because product **2** has two olefin moieties with differing reactivities, this molecule is expected to become a key intermediate in the synthesis of many *gem*-difluoromethylene compounds. Further investigations into the scope and limitations of the present method are expected to expand the potential applications of this approach.

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■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data for the products. 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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■ REFERENCES

(1) For review, see: Ojima, I., Ed.; *Fluorine in Bioorganic and Medicinal Chemistry*; Wiley-Blackwell: London, 2009.
(2) For review, see: Itoh, T. *gem*-Difluorinatedcyclopropanes as key building blocks for novel biologically active molecules. In *Fluorine in Bioorganic and Medicinal Chemistry*; Ojima, I., Ed.; Wiley-Blackwell: London, 2009; pp 313−355.
(3) For review, see: Fedorynski, M. *Chem. Rev.* **2003**, *103*, 1099.
(4) Morikawa, T.; Uejima, M.; Kobayashi, Y. *Chem. Lett.* **1988**, 1407.
(5) (a) Dolbier, W. R., Jr.; Al-Sader, B. H.; Sellers, F.; Koroniak, H. *J. Am. Chem. Soc.* **1981**, *103*, 2138. (b) Dolbier, W. R., Jr. *Acc. Chem. Res.* **1981**, *14*, 195. (c) Tian, S.; Lewis, S. B.; Bartberger, M. D.; Dolbier, W. R., Jr.; Borden, W. T. *J. Am. Chem. Soc.* **1998**, *120*, 6187. (d) Tian, F.; Bartberger, M. D.; Dolbier, R. W., Jr. *J. Org. Chem.* **1999**, *64*, 540.
(6) Gurjar, M. K.; Ravindranadh, S. V.; Sankar, K.; Karmakar, S.; Cherian, J.; Chorghade, M. S. *Org. Biomol. Chem.* **2003**, *1*, 1366.
(7) (a) Mitsukura, K.; Korekiyo, S.; Itoh, T. *Tetrahedron Lett.* **1999**, *40*, 5739. (b) Itoh, T.; Ishida, N.; Mitsukura, K.; Uneyama, K. *J. Fluorine Chem.* **2001**, *112*, 63. (c) Itoh, T.; Ishida, N.; Mitsukura, K.; Hayase, S.; Ohashi, K. *J. Fluorine Chem.* **2004**, *125*, 775.
(8) We chose the benzyl protecting group to facilitate detection of the products.
(9) For recent reviews, see: (a) Zard, S. Z. *Chem. Soc. Rev.* **2008**, *37*, 1603. (b) Quiclet-Sire, B.; Zard, S. Z. *Beilstein J. Org. Chem.* **2013**, *9*, 557.
(10) Fukuyama, T.; Kobayashi, M.; Rahman, Md. T.; Kamata, N.; Ryu, I. *Org. Lett.* **2008**, *10*, 533.
(11) (a) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2039. For recent reviews, see: (b) Deraedt, C.; d'Halluin, M.; Astruc, D. *Eur. J. Inorg. Chem.* **2013**, 4881. (c) Li, H.; Seechurn, C. C. C. J.; Colacot, T. J. *ACS Catal.* **2012**, *2*, 1147.