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Digest paper

Transformations based on ring-opening of *gem*-difluorocyclopropanes

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ABSTRACT

gem-Difluorocyclopropanes are an important fluorinated class of compounds with applications in medicinal chemistry, material sciences and organic synthesis. The transformations based on their ring-opening reactions have been recognized to be useful methods for rapidly synthesizing various fluorinated organic molecules. In this digest paper, we describe these efforts and highlight their powerfully potential and applications as fluorine-containing synthons in organic chemistry.

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Introduction

gem-Difluorocyclopropane is an important fluorinated molecule,[1] in which unique *gem*-difluorosides in the strained ring of cyclopropane bring about a profound effect with respect to its physical properties, chemical reactivities, and especially biological activities.[2,3] For example, *gem*-difluorocyclopropane is a privileged subset of medicinal and bioactive molecules. Many of its derivatives show potential bioactivities such as inhibition of P-glycoproteins,[4] degradation of oncogenic proteins,[5] and insecticidal properties.[6] They also present interesting physical properties as liquid crystalline and polymer materials.[7,8] Consequently, facile and reliable methods access to *gem*-difluorocyclopropanes have been well established. Among them, addition of difluorocarbene to alkenes is one of the most versatile routes to these scaffolds.[9–12]

Compared to the major focus being placed on the diverse biological and physical properties, and on taking them as an interesting synthetic target, however, the chemical reactivities of *gem*-difluorocyclopropanes were less investigated. Ring-opening reactions of *gem*-difluorocyclopropanes are useful transformations to deliver various fluorinated organic molecules. Recently, applications of *gem*-difluorocyclopropanes as fluorine-containing synthons have been paid attention. New reaction patterns with unique reactivity and exceptional selectivity based on them appeared. In particular, those *gem*-difluorocyclopropanes with suitable functional group, such as vinyl, carbonyl, acyloxy, siloxy,

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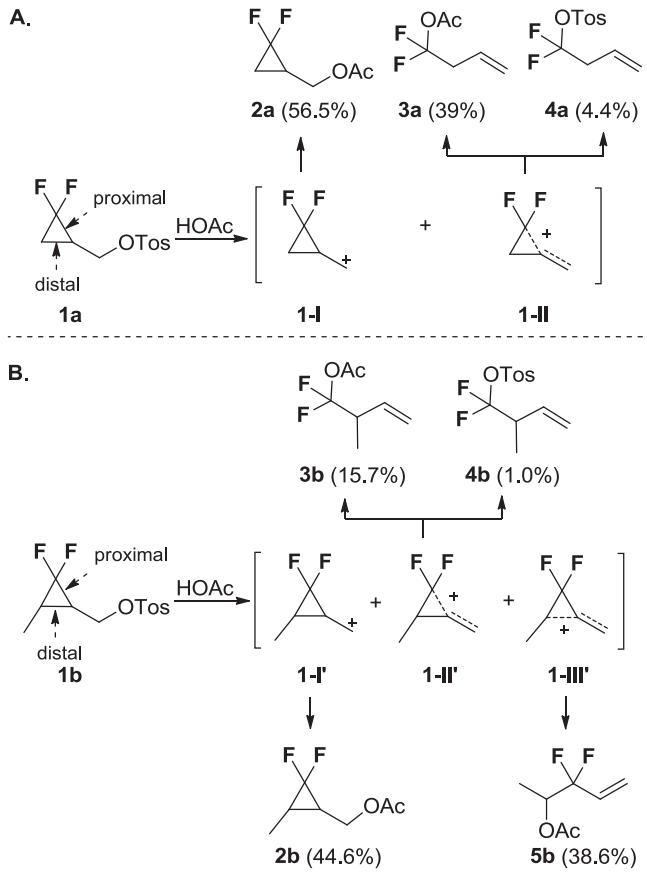
and amido, have exhibited powerful potential of rapidly synthesizing various fluorinated organic molecules.

Several reviews on the chemistry of *gem*-dihalocyclopropanes highlighted the synthesis and applications of *gem*-difluorocyclopropanes. A review in 2003[2] from Dolbier, Jr and Battiste covered the advances of *gem*-difluorocyclopropane chemistry with respect to their structure, synthesis, reactions, and applications before 2002. *gem*-Difluorocyclopropanes are known to facilely decompose thermally due to the higher strain energy of fluorinated cyclopropanes. Earlier investigations on the chemical reactivity of *gem*-difluorocyclopropanes mainly focused on their thermal rearrangement.[13] The homolytic ring-opening pathway has usually been used to understand the behavior of diradicals.[14–16] There has since been a topic on catalytic ring-opening of *gem*-difluorocyclopropanes appeared over ten years, which opens up a new version of their applications in synthesis. This mini-review will give a summary of the ring-opening reactions of *gem*-difluorocyclopropanes, especially emphasizing the transformations of those functionalized ones. The new work developed in our group in this field is also included, while those thermal rearrangement processes reported before 2003 will be excluded. We hope that this review will satisfy the expectations of readers who are interested in the development of this field and looking for up-to-date information on the chemistry of *gem*-difluorocyclopropanes.

Ring-opening of *gem*-difluorocyclopropanes

Besides thermal decomposition, the ring-opening of *gem*-difluorocyclopropanes could be controlled by the catalysts and the reagents. The characters of both catalysts and reagents, the conditions of the reaction, and the anchimeric assistance by functional substituents in substrates proved to determine the mechanism and the regioselectivity of the C—C bond cleavage on three-membered ring.



Scheme 1.

Dolbier Jr. studied the reactivities and regiochemistries of ring-opening of (2,2-difluorocyclopropyl)methyl systems through the acetolysis of tosylates **1a** and **1b** in 2003 (Scheme 1).[17] The computational studies supported the experimental results, and disclosed that ring-opening of **1a** occurred in a regiospecific cleavage of the proximal bond *via* carbocation **1–II** to form ring-opening products **3a** and **4a** (Scheme 1A). By contrast, **1b** with methyl substituent on the ring afforded a mixture of ring-opening products **3b**, **4b** and **5b**, in which product **5b** was obtained as the main ring-opening product by a regioselective distal C—C bond cleavage *via* carbocation **1–III′**.

Recently, Itoh and co-workers reported a regioselective allylation of *gem*-difluorocyclopropanes by reacting bromomethyl *gem*-difluorocyclopropanes **6** with allyltributylstannane in the presence of 2,2′-azobis(isobutyronitrile) (AIBN) leading to 1,6-dienes **7** with a *gem*-difluoromethylene fragment at the allylic position (Scheme 2A).[18] The reaction involves a radical-type distal cleavage followed by a trap of allyltributylstannane. For *gem*-difluorocyclopropanes **8** with *S*-methyl carbonodithioate (-OCS_2Me) as the leaving group, however, the rearrangement of the leaving group competes with the desired allylation to furnish products **7** or **9**, depending on the amount of allyltributylstannane (Scheme 2B).

Konno's group reported a ring-opening reaction of *gem*-difluorocyclopropylstannanes **10** followed by quenching with water, alcohols, carboxylic acids, or tosylamide, providing β-fluoroallylic alcohols **11**, ethers **12**, esters **13**, and amides **14**, respectively, in an exclusively *Z*-selective manner.[19] As described in Scheme 3, the reaction is proposed to undergo the lithium−tin exchange at first to give *gem*-difluorocyclopropyl lithium **3-I**, which may undergo β-elimination to afford monofluorocyclopropene **3-II**. Thermal ring-opening of cyclopropene **3-II** furnishes vinyl carbene[20] intermediate **3-III** which is significantly stabilized by the resonance effect of the aromatic ring. Finally, corresponding β-fluoroallylic alcohols, ethers, esters, and amides **11–14** were obtained by quenching the reaction with various nucleophilic agents.[19,21]

Transition metal-catalyzed cross-coupling reactions provide an important tool for the construction of carbon skeleton, which take place mainly between an electrophilic organohalide and a nucleophile.[22] Recently, Fu's group successfully used *gem*-difluorinated cyclopropanes as coupling partners in transition-metal-catalyzed cross-coupling reaction for the first time.[23] The transformation provides a new catalytic method for ring-opening of *gem*-difluorinated cyclopropanes **15** which have been well applied for the synthesis of a variety of 2-fluoroallylic amines, ethers, esters, and alkylation products **16** by reacting with various nucleophiles. As shown in Scheme 4, the mechanism is proposed to undergo a regioselective distal C—C bond oxidative addition to palladium at first. β-F elimination of the resulting intermediate **4-I** furnishes the 2-fluorinated palladium π–allyl complex **4-II**, from which the external nucleophilic attack occurs at the sterically less hindered C1 atom and affords the desired 2-fluorinated allylic products **16** (Scheme 4). All products **16** were isolated in good to high yields with high *Z*-selectivity.

Very recently, a direct catalytic C–F bond activation of *gem*-difluorocyclopropanes **17** by nickel(II) fluorido complexes was found to evolve ring-opening leading to monofluoroalkenes **18** in good yields and high *Z*-selectivity in the presence of reducing reagent (Scheme 5).[24] Compared with Fu's work,[23] the reaction was proposed to involve a radical based mechanism *via* Ni(I) and NiH complexes as key intermediates.