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Synthesis of Bis- and Oligo-*gem*-difluorocyclopropanes Using the Olefin Metathesis Reaction

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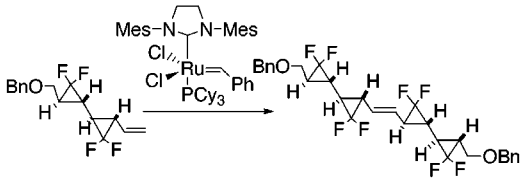
ABSTRACT



Synthesis of six types of novel bis- and oligo-*gem*-difluorocyclopropanes has been accomplished through the olefin metathesis reaction protocol. Two types of ruthenium-based olefin metathesis catalysts were tested: the ruthenium catalyst coordinated with 1,3-dimesityl-4,5-dihydroimidazol-2-ylidene and tricyclohexylphosphine ligands gave better results than the ruthenium catalyst that coordinated with two tricyclohexylphosphine ligands.

Substitution of two fluorine atoms on the cyclopropane ring is expected to alter both chemical reactivity and biological activity as a result of the strong electron-withdrawing nature of fluorine.[1,2] We were attracted by the special property of *gem*-difluorocyclopropanes and accomplished the first synthesis of several types of new *gem*-difluorocyclopropanes in optically pure form.[3,4] As anticipated by the nature of the fluorine atom, the shape of the difluorinated analogue of bicyclopropane 1,6-bis(hydroxymethyl)-2,2,5,5-tetrafluorobicyclopropane (**1**) was slightly different from the simple bicyclopropane **2**. Figure 1 shows the results of the optimized structure of a *gem*-fluorinated bicyclopropane by MO (PM3) calculation.[5] Calculation suggested a kinked form of two difluorocyclopropane groups for compound **1**, while no such twisted form was suggested for bicyclopropane **2**. This was confirmed by results of the CD spectroscopic analysis of optically active **1** in that a large CD spectral change on the Cotton effect was observed.[3b] Even more interesting, the computational chemistry suggested a highly helical shape for oligo-*gem*-difluorcyclopropanes such as pentakis-*gem*-difluorocyclopropane **3**, as shown in Figure 1. Oligo- and poly-*gem*-difluorocyclopropanes are challenging targets for synthetic organic chemists. In this communication, we report our initial results of synthesizing bis- and oligo-*gem*-difluorocyclopropane derivatives through the olefin metathesis reaction strategy.[6,7]

First, we investigated the olefin metathesis reaction of 1-benzyloxymethyl-2,2-difluoro-3-vinylcyclopropane (**5a**) as

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(1) For a review, see: Kitazume, T.; Yamazaki, T. *Topics in Current Chemistry*; Springer-Verlag: New York, 1997; Vol. 193, pp 91−130.

(2) The synthesis of optically active difluorocyclopropane derivatives has recently been reported. (a) Taguchi, T.; Shibuya, A.; Sasaki, H.; Endo, J−i.; Morikawa, T.; Shiro, M. *Tetrahedron; Asymmetry* **1994**, *5*, 1423. (b) Shibuya, A.; Kurishita, M.; Ago, C.; Taguchi, T. *Tetrahedron* **1996**, *52*, 271. (c) Shibuya, A.; Sato, A.; Taguchi, T. *Bioorg. Med. Chem. Lett*. **1998**, *8*, 1979. (d) Kirihara, M.; Takuwa, T.; Kawasaki, M.; Kakuda, H.; Hirokami, S.-I.; Takahata, H. *Chem. Lett.* **1999**, 405. Biological activities were reported for difluorocyclopropane derivatives. (e) Boger, D. L.; Jenkins, T. J. *J. Am. Chem. Soc*. **1996**, *118*, 8860. (f) Taguchi, T.; Kurishita, M.; Shibuya, A.; Aso, K. *Tetrahedron* **1997**, *53*, 9497. (g) Csuk, R.; Eversmann, L. *Tetrahedron* **1998**, *54*, 6445.

(3) (a) Itoh, T.; Mitsukura, K.; Furutani, M. *Chem. Lett*. **1998**, 903. (b) Mitsukura, K.; Korekiyo, S.; Itoh, T. *Tetrahedron Lett*. **1999**, *40*, 5739

(4) Preliminary results of this project have been reported: Itoh, T.; Mitsukura, K.; Ishida, N. The Nagoya COE-RCMS conference, Jan 6−7, 2000, Nagoya, Japan, P32.

(5) MacSpartan Plus was employed for MO (PM3) calculation.

(6) For a review see: Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413.

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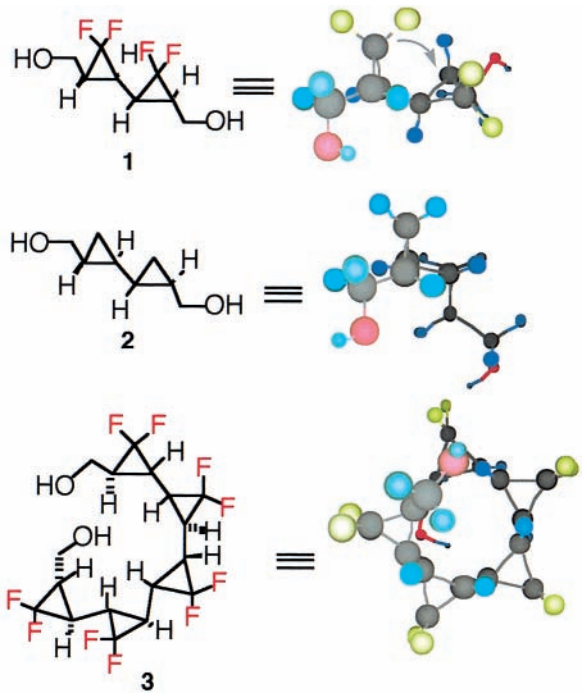
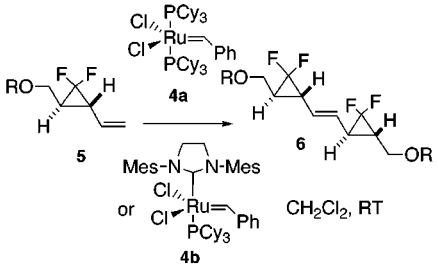


Figure 1. Result of MO (PM3) calculation of oligo-*gem*-difluorocyclopropanes.

a model compound using the Grubbs catalyst, $(PCy_3)_2Cl_2$-Ru=CHPh (**4a**)[6] (Scheme 1). We hoped that the desired

Scheme 1. Synthesis of Bis-*gem*-difluorocyclopropanes



coupling product **6a** would be obtained without difficulty because wide ranging functional group tolerance has been reported for the reaction.[6] However, compound **6a** was obtained in only poor yield (6%) in the presence of 5 mol % of the catalyst, though the stereochemistry of the newly formed olefinic part exhibited perfect (*E*)-selectivity. We tested four solvent systems: dichloromethane (CH_2Cl_2), toluene, benzene, and tetrahydrofuran (THF), and the desired product **6a** was obtained only when the reaction was carried out in CH_2Cl_2 at room temperature; significant decomposition of both substrate and catalyst was observed under elevated temperature conditions. Increasing the amount of the catalyst caused no enhancement of the chemical yield, which remained from 5∼7% even in the presence of 1.0 equiv of the catalyst, and a significant amount of unidentified purple solid was produced. We therefore used a total of 1.0 equiv of the catalyst, adding 20 mol % as a dichloromethane solution (0.01 M) dropwise five times at 12 h intervals.[8] This increased the chemical yield, and the desired coupling product **6a** was obtained in 35% yield. Recently, synthesis of a new ruthenium-based olefin metathesis catalyst **4b** that coordinated with 1,3-dimethyl-4,5-dihydroimidazol-2-ylidene ligand has been reported.[7] Use of the catalyst **4b** gave better results than **4a**, and the metathesis product **6a** was obtained in 31% yield even when just 15 mol % of the catalyst was used, as shown in Table 1 (method A, entry 1). The most drastic increase in chemical yield was recorded when **5c** was subjected to the metathesis reaction; tetrakisdifluorocyclopropane derivative **6c** was obtained in 28% yield using catalyst **4b**, while chemical yield of the metathesis product **6c** was only 9% when a total of 1.0 equiv of the catalyst **4a** was used (five additions of the catalyst **4a** (20 mol %) were made at 12 h intervals).

Fortunately, the olefin metathesis reaction of allylic ether **7a** proceeded successfully to give the coupling product **8a** in efficient yield of 80% using 15 mol % of the commercial catalyst **4a** (method B, entry 4). Three types of metathesis products, **8a**−**c** were obtained in satisfactory yields (entries 4−6). Six types of bis- and oligo-*gem*-difluorinated cyclopropane derivatives were thus synthesized for the first time (Table 1). Substrate **7a** gave the coupling product **8a** in better yield than that of the reaction of substrate **5a**.

It is postulated that decomposition of a metallacyclobutane intermediate like **10** produces ethylene gas and regenerates the ruthenium−carbene complex **11** to complete the catalytic cycle (Figure 2).[6] Because the coupling product **6a** was indeed obtained, though the yield was insufficient, the step to form the key metallacyclobutane **12** and subsequent decomposition might occur smoothly, and it would release

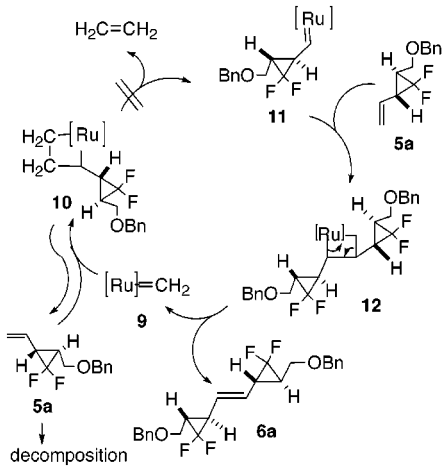
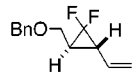
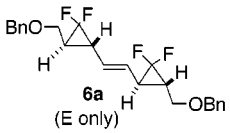
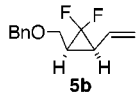
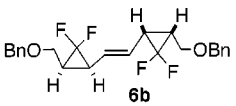
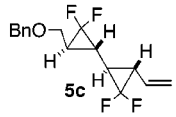
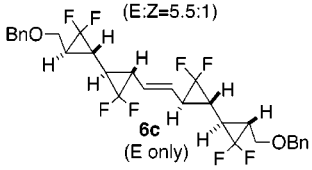
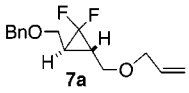
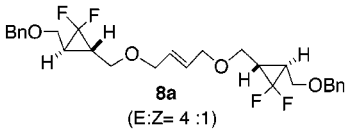
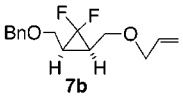
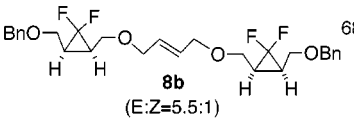
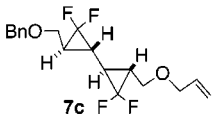
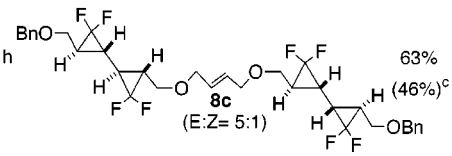


Figure 2. Plausible mechanism of the low chemical yield of the coupling product.

(7) Recent examples: (a) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953. (b) Ulman, M.; Grubbs, R. H. *J. Org. Chem.* **1999**, *64*, 7207.

Table 1. Synthesis of Various *gem*-Difluorocyclopropanes by an Olefin Metathesis Protocol

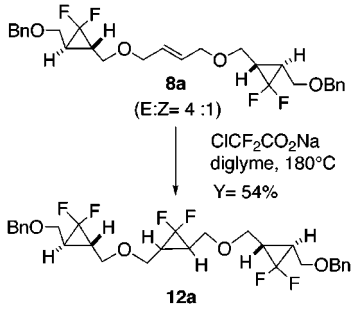
Entry	Substrate	Conditions [a] (Method)	Product (Stereochemistry) [b]	Yield (%)
1	 **5a**	RT, 36 h (A)	 **6a** (E only)	31% (15%)[c] (35%)[d]
2	 **5b**	RT, 36 h (A)	 **6b** (E:Z=5.5:1)	29%
3	 **5c**	RT, 36 h (A)	 **6c** (E only)	28% (9%)[d]
4	 **7a**	RT, 24 h (B)[c]	 **8a** (E:Z= 4 :1)	80%
5	 **7b**	RT, 24 h (B)	 **8b** (E:Z=5.5:1)	68%
6	 **7c**	RT, 36 h (A)	 **8c** (E:Z= 5:1)	63% (46%)[c]

a) **Method A**: Three additions of 5 mol% of the catalyst **4b** solution in CH_2Cl_2 (0.01 M) were made at 12 h intervals. **Method B**: The reaction was carried out in the presence of the whole amount of the catalyst **4a** (15 mol%). b) The ratio of the stereochemistry of the olefinic part was determined by ^1H NMR analysis. c) Three additions of 5 mol% of the catalyst **4a** solution in CH_2Cl_2 (0.01 M) were made at 12 h intervals. d) Five additions of 20 mol% of the catalyst **4a** solution in CH_2Cl_2 (0.01 M) were made at 12 h intervals.

the **6a**−carbene complex **9**. In the present reaction, however, the retro decomposition of metallacyclobutane **10** to vinylcyclopropane **5a** seemed to occur as a result of the strong electron-withdrawing nature of the difluoromethylene moiety, and this stopped the catalytic cycle. Of course, another explanation of the poor results may be possible; since compound **5a** is more sterically bulky at the reaction point than **7a**, this may make it difficult to produce the intermediate **10**. However, this factor seems not as important, because sterically more bulky catalyst **4b** gave better results than did almost all reactions of catalyst **4a**.

All of the products obtained, **6a**−**c** and **8a**−**c**, possess olefinic parts between difluorocyclopropane moieties, so that we are able to add one more difluorocyclopropane group. Trisdifluorocyclopropane (*trans*,*trans*,*trans*)-**12a** was synthesized in 54% yield from **8a** using 50 equiv of difluorocarbene, which was produced by the thermolysis of sodium chlorodifluoroacetate (0.8 mol/L in a diglyme solution) (Scheme 2).

Scheme 2. Synthesis of a Tris-*gem*-difluorocyclopropane



In conclusion, we demonstrated the first synthesis of bis- and oligo-*gem*-difluorocyclopropane derivatives via an olefin metathesis reaction methodology. This reaction is applicable

(8) It was essential to use the catalyst as a CH_2Cl_2 solution. No increase of the chemical yield was observed when the catalyst powder was added to the reaction mixture in a 5-fold portion.

for the synthesis of an optically active derivative of which optically active starting materials have already been synthesized.[3] Further investigations to improve the reaction efficiency by changing the catalyst and synthesizing hybrid types of poly-*gem*-difluorcyclopropanes are ongoing.

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Supporting Information Available: Experimental details on the synthesis of **6a** and **8a**, as well as spectroscopic data for selected compounds. This information is available free of charge via the Internet at http://pubs.acs.org.

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