ORGANIC LETTERS

2008
Vol. 10, No. 5
769−772

Boron-Substituted Difluorocyclopropanes: New Building Blocks of *gem*-Difluorocyclopropanes

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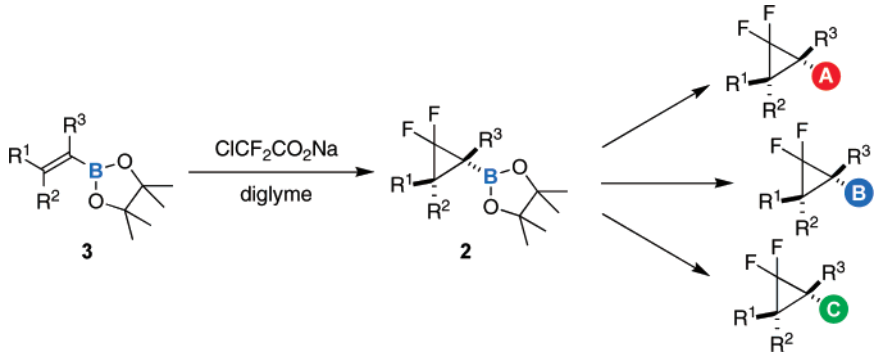
Received November 26, 2007

ABSTRACT



Cycloaddition of difluorocarbene to alkenyl boronates 3 gave boron-substituted *gem*-difluorocyclopropanes 2 in stereospecific fashion. Upon treatment with lithium carbenoids, cyclopropyl boronates 2 underwent one-carbon homologation to afford a variety of *gem*-difluorocyclopropanes in good yields.

Organofluorine compounds are widely used in the medicinal, agricultural, and material sciences.[1] In particular, fluorine-containing cyclopropanes have received a great deal of attention due to their biological activities. For instance, sitafloxacin (DU-6859a) which has a fluorocyclopropyl moiety is a quinolone antimicrobial agent.[2] Zosuquidar trihydrochloride (LY335979·3HCl) possessing a *gem*-difluorocyclopropane framework has been studied for its ability to reverse resistance to chemotherapy.[3] Certain *gem*-difluorocyclopropane derivatives show potentially unique biological activities such as degradation of oncogenic proteins,[4] DNA alkylation,[5,6] and insecticidal properties.[7] In recent

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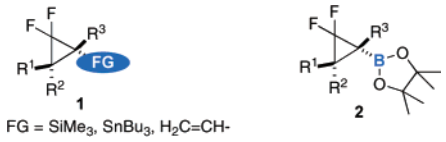
10.1021/ol702851t CCC: $40.75
Published on Web 01/29/2008

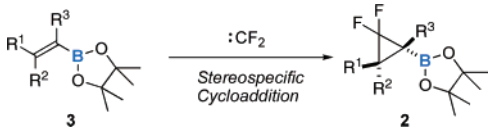
years, introducing difluorocyclopropyl moieties into biomolecules such as nucleosides[8,9] and amino acids[10] has been a topic of considerable interest. Furthermore, transformations involving regioselective ring-opening of *gem*-difluorocyclopropanes provides a variety of useful fluoroorganic compounds.[11−14] Therefore, the development of general building blocks for *gem*-difluorocyclopropanes is of significant importance.

One of the useful difluorocyclopropane building blocks is a difluorocyclopropyl anion equivalent, which can react with various electrophiles. It is known that deprotonation of *gem*-difluorocyclopropanes upon exposure to organolithium reagents procceeds even at low temperature. However, the resultant anions possessing lithium as a counterion are too unstable to suppress facile β-fluoride elimination.[15] To avoid defluorination from difluorocyclopropyl moieties, Taguchi developed the reactions of silyl-substituted difluorocyclopropanes with aldehydes in the presence of a catalytic amount of fluoride anion to give the corresponding cyclopropylcarbinols successfully (Scheme 1).[16] Besides silyl substituents, stannyl[17] and vinyl groups are useful functionalities for transition-metal-catalyzed transformations such as alkene metathesis.[18] Taking advantage of broad synthetic utility of organoboron compounds,[19] boryl-substituted difluorocyclopropanes are considered to be versatile building blocks which provide a variety of *gem*-difluorocyclopropanes.[20−22] Herein, we present a stereospecific preparation and synthetic applications of boryl-substituted difluorocyclopropanes **2**, new *gem*-difluorocyclopropane building blocks (Scheme 2).

Scheme 1



Scheme 2



When 1-phenylvinylboronic acid pinacol ester (**3a**) was treated with sodium chlorodifluoroacetate[23] (8 equiv to **3a**) in diglyme at 180 °C for 15 min (Method A), cycloaddition of difluorocarbene to **3a** took place to afford (2,2-difluoro-1-phenylcyclopropyl)borate **2a** in 61% yield (entry 1 in Table 1). As a source of difluorocarbene[24] in this case, the use of sodium chlorodifluoroacetate gave a better result than that of trimethylsilyl fluorosulfonyldifluoroacetate (TFDA)/NaF system[25] (14% yield). Other examples of the formation of boryl difluorocyclopropanes **2** are given in Table 1. The reactions of 1-substituted vinylboronic esters **3b** and **3c** possessing alkyl and alkoxymethyl groups[26] also gave the

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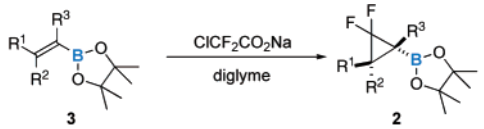
Table 1. Synthesis of Boron-Substituted Difluorocyclopropanes



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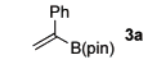
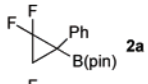
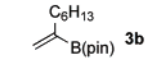
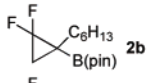
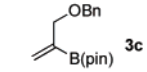
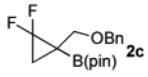
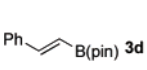
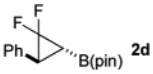
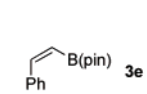
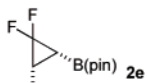
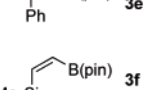
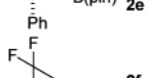
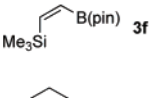
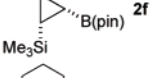
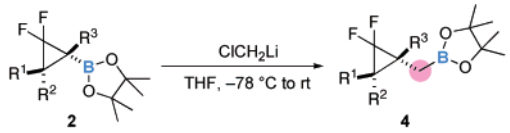
1	 3a	 2a	A B	61 71
2	 3b	 2b	A	80
3	 3c	 2c	A	59
4	 3d	 2d	A B	14[d] 50
5	 3e	 2e	B	71
6[e]	 3f	 2f	B	46
7	 3g	 2g	B	74

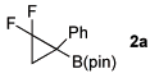
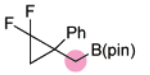
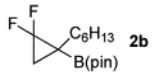
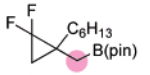
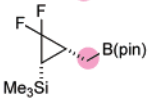
[a] pin = $-OCMe_2CMe_2O-$. [b] The reaction was carried out using $ClCF_2CO_2Na$ (8 equiv) for 15 min (Method A) or using $ClCF_2CO_2Na$ (3−4 equiv) for 5−8 h (Method B). [c] Isolated yield. [d] Determined by ^1H NMR analysis. [e] $ClCF_2CO_2Na$ (8 equiv) was used.

corresponding adducts in 80% and 59% yields, respectively (entries 2, 3). In general, cycloaddition reactions of difluorocarbene to alkenes proceed in a stereospecific manner. The use of (*E*)- and (*Z*)-alkenyl borates such as **3d**−**f**[27,28] is anticipated to deliver *cis*- and *trans*-substituted boryl cyclopropanes **2d**−**f**. However, the reactivities of alkenyl borates **3d**−**f** were too low to obtain the desired adducts **2d**−**f** (<15% yields, 180 °C, 15 min) due to the electronic effect of boryl groups. According to Barnett's modification,[3b] a slow addition technique worked well for difluorocyclopropanation of vicinal disubstituted alkenes **3d**−**f**; the yields of **2d**−**f** were improved to 50%, 71%, and 46%, respectively, when the reactions were carried out at 180 °C along with adding diglyme solution of sodium chlorodifluoroacetate over the course of 8 h by the use of syringe pump (Method B, entries 4−6). Cyclic (trisubstituted) boronate **3g**[26] also underwent difluorocyclopropanation to form the fused ring system **2g** in 74% yield. Combined with well-established protocols for regio- and stereoselective synthesis of alkenyl borates **3**,[26−28] difluorocyclopropanation of **3** gave new borylated building blocks **2** in high stereochemical fidelity.

Next, we explored selective transformations of boryl functionalities in difluorocyclopropanes **2**. In particular, the synthetically useful application of boryl difluorocyclopropanes **2** has been made for one-carbon homologation using lithium carbenoids.[29−32] Treatment of **2a** with chloromethyllithium (1.3 equiv) in THF at −78 °C followed by warming to room-temperature gave homologated boronic ester **4a** in 95% yield (Table 2, entry 1). Under similar reaction conditions, boronic esters **2b** and **2f** also gave the corresponding cyclopropylmethyl borates **4** in good yields (entries 2 and 3 in Table 2). In each case, the one-carbon homologation proceeded smoothly in a highly controlled manner. Noteworthily, neither cleavage of the difluorocyclopropane rings nor dehydrofluorination was observed upon exposure to carbanionic reagents (lithium carbenoids).

Table 2. One-Carbon Homologation of Borates **2**

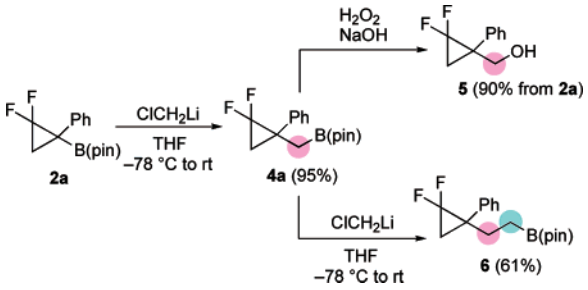


entry	substrate 2[a]	homologation product 4	% yield[b]
1	 2a	 4a	95
2	 2b	 4b	86
3	 2f	 4f	77

[a] pin = $-OCMe_2CMe_2O-$. [b] Isolated yield

One-carbon homologation of boryl difluorocyclopropanes **2** was combined with H_2O_2/NaOH oxidation (Scheme 3).[33]

Scheme 3



Without isolation of the intermediate **4a**, cyclopropyl boronate **2a** was converted cleanly to (difluorocyclopropyl)methanol **5** in 90% overall yield. Furthermore, cyclopropylmethyl borate **4a** reacted with chloromethyllithium (1.3

(27) Preparation of (*E*)-alkenylboronic esters: (a) Pereira, S.; Srebnik, M. *Organometallics* **1995**, *14*, 3127−3128. (b) Wang, Y. D.; Kimball, G.; Prashad, A. S.; Wang, Y. *Tetrahedron Lett.* **2005**, *46*, 8777−8780.

(28) Preparation of (*Z*)-alkenylboronic esters: Deloux, L.; Srebnik, M. *J. Org. Chem.* **1994**, *59*, 6871−6873.

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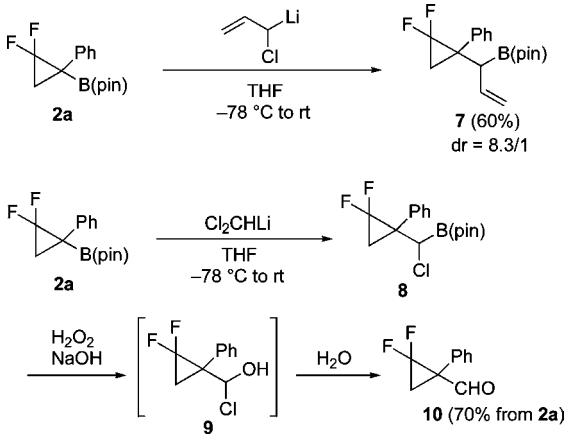
equiv) in THF to afford cyclopropylethyl borate **6** in 61% yield. Thereby, stepwise two-carbon homologation[34] of boryl difluorocyclopropane **2a** was achieved with these operations proceeding without incident.

Various lithium carbenoids are applicable for homologation of (difluorocyclopropyl)borates **2** (Scheme 4). An allylic

Scheme 4



borate functionality[35] was constructed by the use of α-chloroallyllithium.[36] Addition of α-chloroallyllithium to a THF solution of **2a** at −78 °C gave the homologated α-vinylboronate **7** as a mixture of diastereomers (8.3/1). On the other hand, the use of dichloromethyllithium allowed the insertion of a chloromethyl group into the C−B bond in **2a** to form borate **8**. α-Chloroboronic ester **8** was oxidized by H_2O_2/NaOH to provide chloroacetal intermediate **9**,[37] which was readily converted to aldehyde **10** in 70% overall yield from **2a**. Formally, the transformation of the boronate moiety in **2a** to a formyl group was successfully accomplished via the reaction sequence.

In conclusion, we have disclosed the first synthesis of boron-substituted *gem*-difluorocyclopropanes **2** in a stereospecific fashion. To demonstrate the synthetic utility of boryl functionalities in **2**, homologation with lithium carbenoids and the subsequent oxidation afforded a variety of *gem*-difluorocyclopropanes. Further studies such as asymmetric synthesis of boryl difluorocyclopropanes **2** are underway to explore the useful applications.

Acknowledgment. This work is dedicated to the late Professor Yoshihiko Ito. The financial support of the Ministry of Education, Culture, Sports, Science and Technology of Japan (Grant-in-Aid for Scientific Research (B), No. 18350054 and Grant-in-Aid for Scientific Research on Priority Areas "Chemistry of Concerto Catalysis", No. 19028046) is gratefully acknowledged. We thank Prof. Masahiko Hayashi (Kobe University) for his useful suggestions.

Supporting Information Available: Details of experimental procedures and characterization data (^{1}H, ^{13}C, and ^{19}F NMR, IR, and mass spectrometry) for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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