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Stereoselective Generation of (*E*)- and (*Z*)-2-Fluoroalkylidene-Type Carbenoids from (2-Fluoro-1-alkenyl)iodonium Salts and Their Application for Stereoselective Synthesis of Fluoroalkenes

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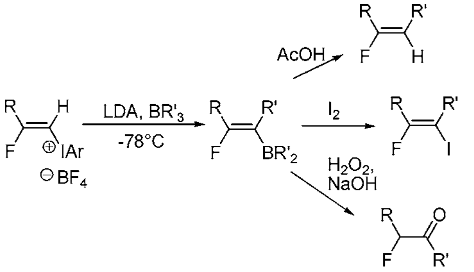
ABSTRACT



Alkylidene-type carbenoids, generated from (*Z*)- or (*E*)-(2-fluoro-1-alkenyl)iodonium salts by treatment with LDA, reacted with trialkylboranes to give (*E*)- or (*Z*)-(fluoroalkenyl)boranes stereoselectively. The resulting (fluoroalkenyl)borane can be used for the selective synthesis of (*E*)- or (*Z*)-fluoroalkenes, (*E*)- or (*Z*)-fluoroiodoalkenes, and α-fluoroketones.

Alkylidene-type carbenoids, 1-halo-1-metalo-1-alkenes, have been used for C−C bond formations[1] or 1,1-dimetalo-1-alkene synthesis.[2] They can be generated by halogen−metal exchange from 1,1-dihalo-1-alkenes or by hydrogen−metal exchange from 1-halo-1-alkenes.[1,2] However, a strong base, such as an alkyllithium, is necessary for their generation, and stereoselective preparation of the alkylidene-type carbenoids was difficult.[1]

On the other hand, an α-proton of alkenyliodonium salts is acidic and can be abstracted by a relatively weak base. The resulting alkylidenecarbenes change to cyclopentene derivatives by an intermolecular C−H insertion reaction or to alkynes by a 1,2-migration reaction.[3] However, alkylidene-type carbenoids, their precursors, have not been used for organic synthesis.[4] Recently, we succeeded in the stereoselective synthesis of both (*E*)- and (*Z*)-(2-fluoro-1-alkenyl)iodonium salts (**1**)[6] and used them for the stereoselective

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(1) (a) Braun, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 430. (b) Kasatkin, A.; Whitby, R. J. *Tetrahedron Lett.* **1997**, *38*, 4857. (c) Kasatkin, A.; Whitby, R. J. *J. Am. Chem. Soc.* **1999**, *121*, 7039.

(2) (a) Hata, T.; Kitagawa, H.; Masai, H.; Kurahashi, T.; Shimizu, M.; Hiyama, T. *Angew. Chem., Int. Ed.* **2001**, *40*, 790. (b) Kurahashi, T.; Hata, T.; Masai, H.; Kitagawa, H.; Shimizu, M.; Hiyama, T. *Tetrahedron* **2002**, *58*, 6381.

(3) (a) Ochiai, M.; Takaoka, Y.; Nagao, Y. *J. Am. Chem. Soc.* **1988**, *110*, 6565. (b) Ochiai, M.; Kunishima, M.; Tani, S.; Nagao, Y. *J. Am. Chem. Soc.* **1991**, *113*, 3135. (c) Ochiai, M.; Uemura, K.; Masaki, Y. *J. Am. Chem. Soc.* **1993**, *115*, 2528. (d) Sueda, T.; Nagaoka, T.; Goto, S.; Ochiai, M. *J. Am. Chem. Soc.* **1996**, *118*, 10141.

(4) The presence of the alkylidene-type carbenoids (alkylidenecarbene-iodonium ylides) as the precursor of alkylidenecarbene was shown by H−D exchange at the α-proton of alkenyliodonium salts under basic conditions.[5]

(5) (a) Ochiai, M.; Kunishima, M.; Fuji, K.; Shiro, M.; Nagao, Y. *Chem. Commun.* **1988**, 1076. (b) Stang, P. J.; Wingert, H.; Arif, A. M. *J. Am. Chem. Soc.* **1987**, *109*, 7235.

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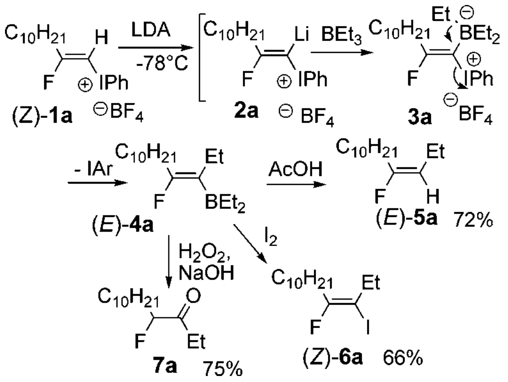
synthesis of various fluoroalkenes.[7] During our continuous study of the stereoselective synthesis of fluoroalkenes using **1**, we found that the 2-fluoroalkylidene-type carbenoids (**2**) can be generated from **1** by treatment with LDA at low temperature and used for the reaction with trialkylboranes to give (*E*)- or (*Z*)-(fluoroalkenyl)boranes (**4**) stereoselectively. The resulting (fluoroalkenyl)borane **4** can be used for the selective synthesis of (*E*)- or (*Z*)-fluoroalkenes (**5**), (*E*)- or (*Z*)-fluoroiodoalkenes (**6**), and α-fluoroketones (**7**).

When a mixture of (*Z*)-(2-fluoro-1-dodecenyl)iodonium salt ((*Z*)-**1a**) and Et_3B in THF was treated with LDA at −78 °C, followed by AcOH, (*E*)-4-fluoro-3-tetradecene ((*E*)-**5a**) was stereoselectively obtained in 72% yield (Scheme 1).[8]

Scheme 1



The formation of (*E*)-(1-ethyl-2-fluoro-1-dodecenyl)diethylborane ((*E*)-**4a**) as a precursor of (*E*)-**5a** was shown by the following results. The replacement of AcOH by CD_3-COOD gave (*E*)-3-deuterio-4-fluoro-3-tetradecene. The treatment of the reaction mixture with I_2 gave (*Z*)-4-fluoro-3-iodo-3-tetradecene ((*Z*)-**6a**),[10] an iodination product of **4a**, in 66% yield.[11] The oxidation of **4a** with H_2O_2 gave 4-fluoro-3-tetradecanone (**7a**) in 75% yield.

When a mixture of (*E*)-(2-fluoro-1-dodecyl)iodonium salt ((*E*)-**1a**) and Et_3B was treated with LDA as in the case of (*Z*)-**1a**, the expected (*Z*)-4-fluoro-3-tetradecene ((*Z*)-**5a**) was stereoselectively obtained; however, the yield was low, and a significant amount of 3-tetradecyne was also formed. As the fluoride and the borane occupy the trans configuration on the double bond, (*Z*)-**4a** is less stable than (*E*)-**4a**, and under the reaction conditions, elimination takes place to give 3-tetradecyne. The problem could be overcome by carrying out the reaction at lower temperature (−90 °C), and (*Z*)-**5a** could be obtained in 61% yield (Scheme 2).[8] Thus, (*E*)- and (*Z*)-**5a** could be stereospecifically prepared from (*Z*)- and (*E*)-**1a**, respectively. If the alkylidene carbenes were generated under the reaction conditions, the observed stereospecificity could not be explained. Therefore, Et_3B reacted with carbenoids (**2**), generated by the reaction of **1** with LDA, before decomposition to the carbenes, and (*E*)- or (*Z*)-**4a** was stereospecifically formed as shown in Schemes 1 and 2.[13] (*E*)-4-Fluoro-3-iodo-3-tetradecene ((*E*)-**6a**) was also stereoselectively obtained in 52% yield by treatment with I_2 as in the case of (*Z*)-**6a**.

Scheme 2

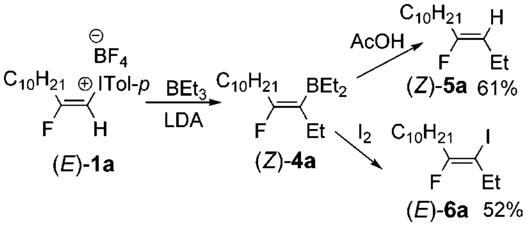
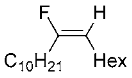
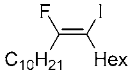
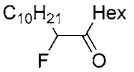
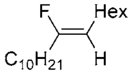
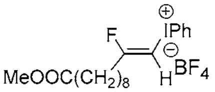
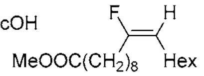


Table 1. Reaction of Trihexylborane with Carbenoids Generated from Alkenyliodonium Salts

alkenyliodonium salts	reagent	product	yield (%)[a]
(*Z*)-**1a**	AcOH	 (*E*)-**5b**	72
(*Z*)-**1a**	ICl AcONa	 (*Z*)-**6b**	65
(*Z*)-**1a**	H_2O_2 NaOH	 **7b**	82
(*E*)-**1a**	AcOH	 (*Z*)-**5b**	70
 (*Z*)-**1b**	AcOH	 (*E*)-**5c**	71

[a] Isolated yield based on alkenyliodonium salt.

When Hex_3B was used for the reaction with **1a**, the corresponding (*E*)- or (*Z*)-8-fluoro-7-octadecene ((*E*)-**5b** or (*Z*)-**5b**), (*Z*)-8-fluoro-7-iodo-7-octadecene ((*Z*)-**6b**), and 8-fluoro-7-octadecanone (**7b**) were selectively obtained. Application of a functionalized (fluoroalkenyl)iodonium salt (**1b**)

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(6) As for the synthesis of (*E*)-(2-fluoro-1-alkenyl)iodonium salts, see: (a) Hara, S.; Yoshida, M.; Fukuhara, T.; Yoneda, N. *Chem. Commun.* **1998**, 965. (b) Yoshida, M.; Kawakami, K.; Hara, S. *Synthesis* **2004**, 2821. As for the synthesis of (*Z*)-(2-fluoro-1-alkenyl)iodonium salts, see: (c) Yoshida, M.; Hara, S. *Org. Lett.* **2003**, *5*, 573.

(7) Hara, S. In *Fluorine-Containing Synthons*; Soloshonok, V. A., Ed.; American Chemical Society: Washington, DC, 2005; p 120.

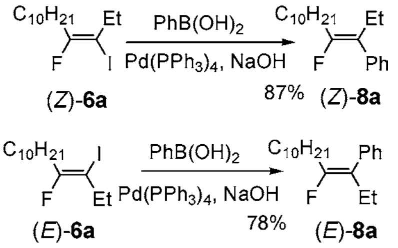
(8) A J_{H-F} on a double bond in (*E*)-**5a** was smaller than that of (*Z*)-**5a** which shows that H and F on a double bond have a cis configuration in (*E*)-**5a**.[9]

(9) Everett, T. S. In *Chemistry of Organic Fluorine Compounds II*; Hudlicky, M., Pavlath, A. E., Eds.; American Chemical Society: Washington, DC, 1995; p 1042.

(10) Brown, H. C.; Hamaoka, T.; Ravindran, N. *J. Am. Chem. Soc.* **1973**, *95*, 5786.

(11) ^{19}F NMR of (*Z*)-**6a** appeared at −75 ppm, and on the other hand, that of (*E*)-**6a** appeared at −95 ppm which is in good agreement with previously reported data for (*Z*)- and (*E*)-fluoroiodoalkenes.[12]

Scheme 3



was also possible, and the fluoroalkene having an ester group ((*E*)-**5c**) could be obtained as shown in Table 1.

Trisubstituted fluoroalkenes (**8a**), which are difficult to prepare by the conventional methods,[7] could be stereoselectively prepared from (*Z*)-**6a** or (*E*)-**6a** by applying them to the Suzuki–Miyaura coupling reaction.[14] Thus, in the presence of a Pd catalyst and a base, the cross-coupling reaction of (Z)-**6a** with phenylboronic acid took place to give (*Z*)-4-fluoro-3-phenyl-3-tetradecene (*Z*)-**8a** stereoselectively. Similarly, (*E*)-**8a** could be obtained from (*E*)-**6a** as shown in Scheme 3. Their stereochemistry was determined from NOEs of ^{1}HNMR analysis.

Supporting Information Available: Details of experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Zupan, M. *Synthesis* **1976**, 473.
(13) Zweifel, G.; Fisher, R. P.; Snow, J. T.; Whitney, C. C. *J. Am. Chem. Soc.* **1971**, *93*, 6309.
(14) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.