Chapter 5

Stereoselective Synthesis of Monofluoroalkenes Using Cross-Coupling Reactions

Shoji Hara

Division of Molecular Chemistry, Graduate School of Engineering, Hokkaido University, Sapporo 060–8628, Japan

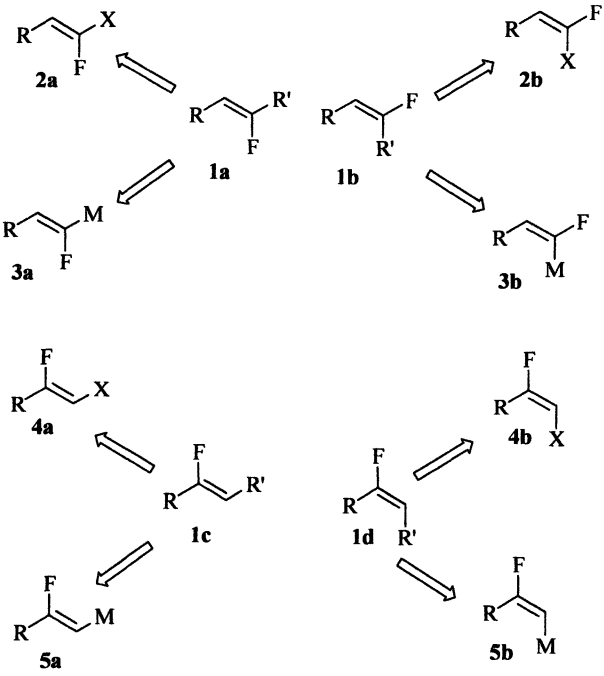
Various methods for the stereoselective synthesis of fluorohaloalkenes and fluoroalkenyl metals are developed. The resulting fluorohaloalkenes and fluoroalkenyl metals are used for the cross-coupling reaction to synthesize monofluoroalkenes stereoselectively. The cross-coupling reactions using fluorohaloalkenes and fluoroalkenyl metals are a powerful tool for the stereoselective synthesis of polyfunctionalized fluoroalkenes and alkadienes.

Introduction

Introduction of a fluorine atom onto the double bond of natural compounds having interesting bioactivities is of great interest because the fluorine atom can enhance their bioactivities or reduce their undesired side-effects (*1-3*). The Horner-Wadsworth-Emmons reaction has been generally used for the stereoselective synthesis of fluoroalkenes (*4*). The reaction of a fluorophosphonate with aldehydes provides (*E*)-α-fluoro-α,β-unsaturated esters stereoselectively. However, in order to introduce the fluorine atom onto any position of the double bond in natural products, more methods for the selective synthesis of fluoroalkenes are desired.

In Fluorine-Containing Synthons; Soloshonok, Vadim A.;
ACS Symposium Series; American Chemical Society: Washington, DC, 2005.

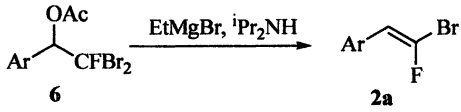
On the other hand, cross-coupling reactions using transition metal catalysts have been recently used as a powerful tool for the stereoselective synthesis of polyfunctionalized alkenes and alkadienes (*5,6*). For the synthesis of various monofluoroalkenes (**1a-d**) by the cross-coupling reactions, stereoselective synthesis of fluorohaloalkenes (**2**) or (**4**), or fluoroalkenyl metals (**3**) or (**5**) is required (Scheme 1).



Scheme 1 R = aryl, alkyl, alkenyl
R' = aryl, alkyl, alkenyl, ester

Stereoselective Synthesis of 1-Fluoro-1-haloalkenes (2) and their Application to the Cross-coupling Reactions.

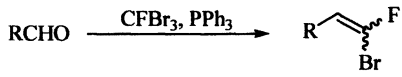
Hiyama *et al.* reported that (*E*)-1-bromo-1-fluoroalkenes **2a** (R = Ar, X = Br) can be stereoselectively prepared from aldehyde-dibromofluoromethyllithium adducts (**6**) by reductive elimination reaction (*7*) (Scheme 2).



Scheme 2

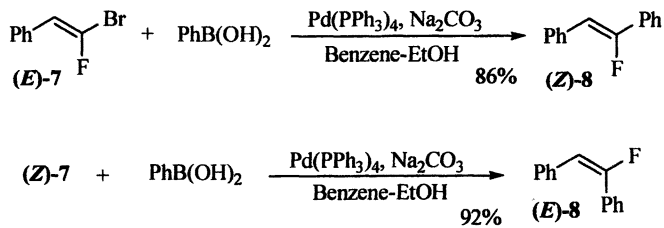
Rolando *et al.* modified this methodology and used it for the synthesis of fluorinated analogs (**9**) and (**10**) of resveratrol and pterostilbene (*16*). A β-bromo-β-fluorostyrene derivative (**11**) was obtained as a mixture of stereoisomers from the 3,5-dihydroxybenzaldehyde derivative by a modified Burton method. Suzuki-Miyaura coupling reaction of **11** with phenylboronic acid derivative (**12**) gave the (*Z*)-isomer of fluororesveratrol derivative (**13**) selectively. Deprotection of **13** gave the desired fluorinated analog **9** of resveratrol. They also synthesized **10** using phenylboronic acid derivative (**14**) and bromofluorostyrene derivative (**15**) (Scheme 6).

Generally, 1-bromo-1-fluoro-1-alkenes (**2**, X = Br) have been prepared by the reaction of aldehydes with $CFBr_3$ and Ph_3P (*4,8,9*). However, a mixture of (*E*)- and (*Z*)-isomers was formed and their separation is practically difficult (Scheme 3). Several methods have been reported for the isomerization of the (*Z*)-isomer to the more stable (*E*)-isomer (*10-12*).



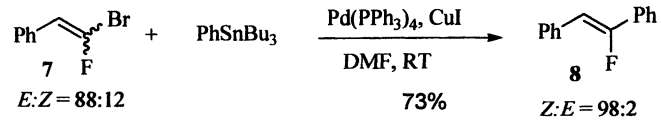
Scheme 3

McCarthy *et al.* separated both isomers of β-bromo-β-fluorostyrene (**7**) by gas chromatography and used them for the Suzuki-Miyaura coupling reaction to give (*Z*)- and (*E*)-fluorostilbenes (**8**) stereospecifically (*10,13*) (Scheme 4).

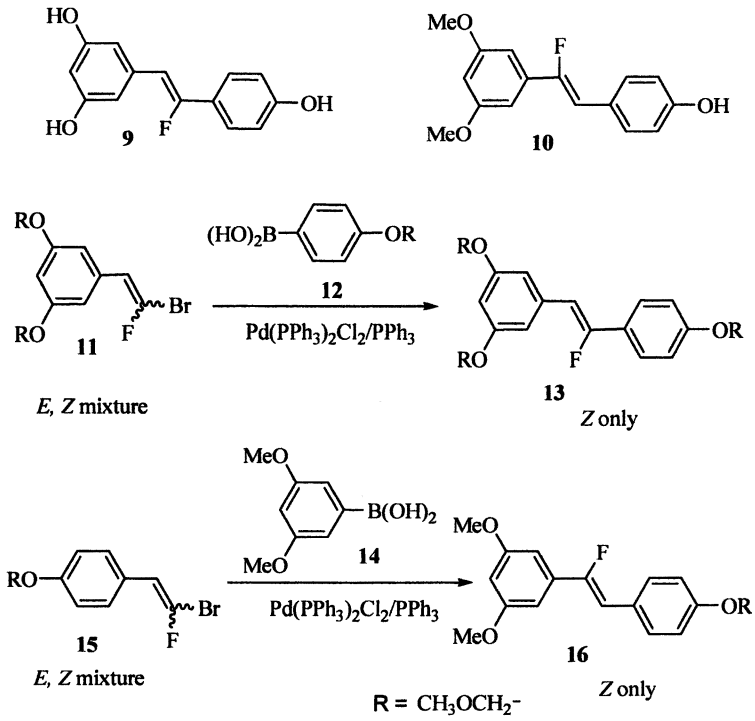


Scheme 4

In order to synthesize cross-coupling products derived from the (*E*)-isomer (**2a**, X = Br), the mixture can be used without separation, because the (*E*)-isomer reacts more rapidly than the (*Z*)-isomer (*14,15*). For instance, (*Z*)-fluorostilbene **8** could be stereoselectively synthesized from a mixture of (*E*)- and (*Z*)-**7** by the Stille coupling reaction (*12*) (Scheme 5).

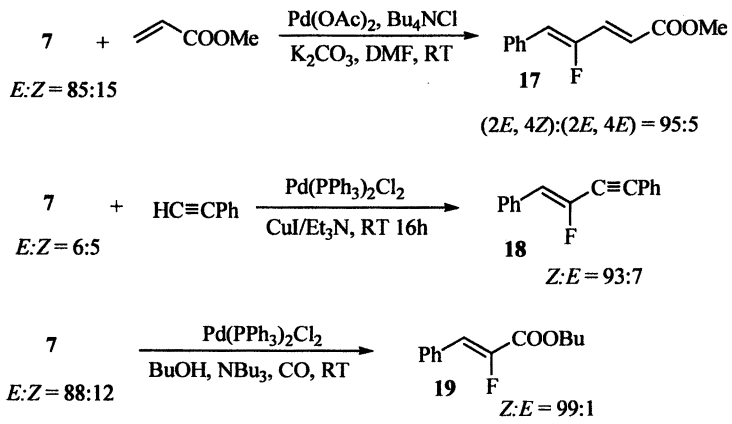


Scheme 5



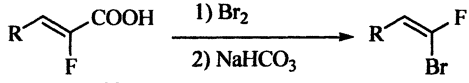
Scheme 6

This methodology is also applicable for other cross-coupling reactions such as the Heck reaction, Sonogashira reaction, and alkoxycarbonylation reaction. From an (*E*)- and (*Z*)-mixture of β-bromo-β-fluorostyrene **7**, (2*E*, 4*Z*)-γ-fluoro-α,β,γ,δ-unsaturated ester (**17**), (*Z*)-fluoroenyne (**18**), and (*Z*)-α-fluoro-α,β-unsaturated ester (**19**) were stereoselectively prepared (*17,15,18*) (Scheme 7).



Scheme 7

On the other hand, pure (*Z*)-1-fluoro-1-bromoalkenes (**2b,** X = Br) can be prepared from (*Z*)-α-fluoro-α,β-unsaturated carboxylic acids (**20**) by bromination and decarboxylative hydrogen bromide elimination sequences (*11*) (Scheme 8).



20

Scheme 8

Rolando *et al.* used (*Z*)-**7** obtained by this method for the Sonogashira reaction, Heck reaction, and Stille reaction, and succeeded in the stereoselective synthesis of (*E*)-fluoroenyne (**21**), (2*E,* 4*E*)-γ-fluoro-α,β,γ,δ-unsaturated ester (**22**), (*E*)-fluorodiene (**23**), respectively (*11,19*) (Scheme 9).

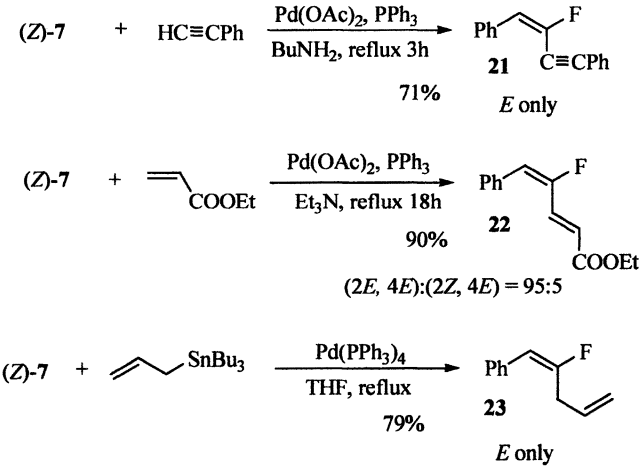
However, this method is effective only when R in Scheme 8 is an aromatic group having no electron-donating substituent. When R is an aliphatic group or an aromatic group having the electron-donating group, good stereoselectivity cannot be expected. Burton *et al.* reported that pure **2b** (X = Br) is obtainable by a kinetic separation method. When a mixture of **7** was used for the cross-coupling reactions, (*E*)-**7** reacted selectively and (*Z*)-**7** remained unchanged (*14*). Therefore, after the coupling reaction, (*Z*)-**7** can be easily separated from the mixture, and (*E*)-fluoroenyne (**21**) was stereoselectively prepared using (*Z*)-**7** obtained by the kinetic separation method (*15*). More conveniently, (*E*)-**7** in the mixture was selectively reduced to the fluoroalkene, and the remained (*Z*)-**7** was used for the alkoxycarbonylation reaction without separation to give (*E*)-α-fluoro-α,β-unsaturated esters (**24**) stereoselectively (*18*) (Scheme 10)

Synthesis of 1-Fluoro-1-alkenyl Metals (3) and their Application to the Cross-coupling Reactions

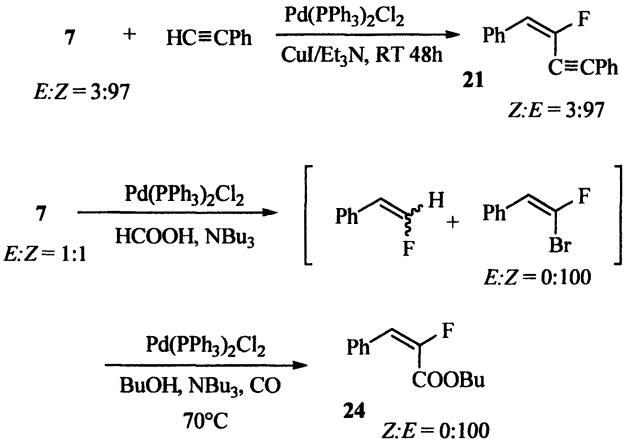
(1-Fluoro-1-alkenyl)tributylstannane (**26**) was non-stereoselectively synthesized from aldehydes in two-steps *via* (fluoroalkenyl)sulfone (**25**). It was used for the further reactions after separation by column chromatography (*20*) (Scheme 11).

(*E*)-(1-Fluoro-2-phenylvinyl)tributylstannane (**27**) was used for the cross-coupling reaction with 5-iodo-1,3-dimethyluracil (**28**) and benzoyl chloride to give (*Z*)-5-(1-fluoro-2-phenylvinyl)-1,3-dimethyluracil (**29**) and fluorochalcone (**30**) respectively (*21,22*) (Scheme 12).

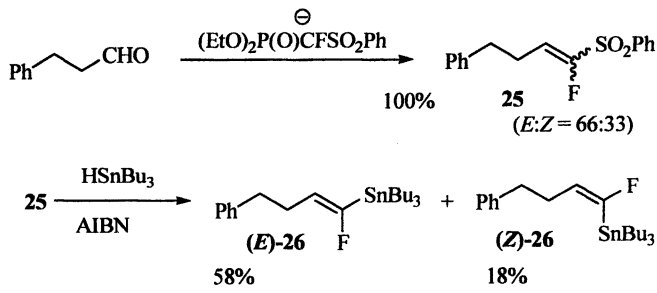
A polyfunctionalized fluorochromone derivative (**33**) was synthesized from formylchromone derivative (**31**) by this methodology. (Fluorovinyl)stannane (**32**) was synthesized from **31** via a fluorosulfone, and (*E*)-**32** was used for the cross-coupling reaction with β-iodoacrylate to give **33** stereoselectively (*22*) (Scheme 13)



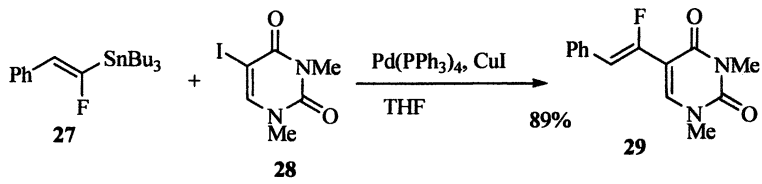
Scheme 9

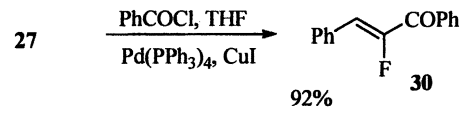


Scheme 10

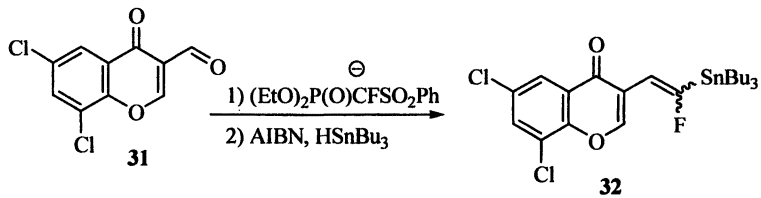


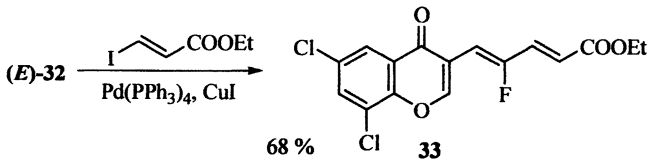
Scheme 11





Scheme12



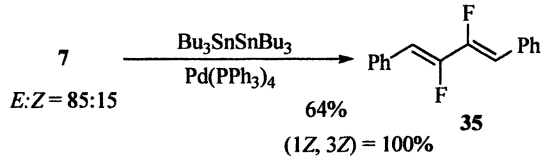


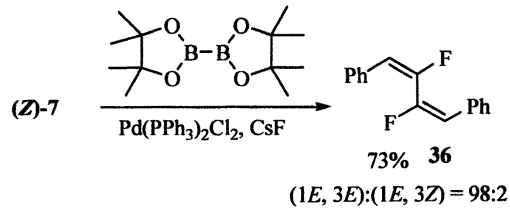
Scheme13

No other successful methods for the synthesis of 1-fluoro-1-alkenyl metals (**3**) have been reported. The reaction of β-bromo-β-fluorostyrene **7** with bis(tributyltin) or bis(pinacolato)diboron for the synthesis of **27** or (*E*)-1-fluoro-1-alkenylborane (**34**) resulted unsuccessfully (*23,24*). A homo coupling product (**35**) or (**36**) was obtained instead of the expected **27** or **34**. The cross-coupling reaction between the generated **27** or **34** with **7** must be fast and it is difficult to terminate the reaction at the formation of **27** or **34** (Scheme 14).

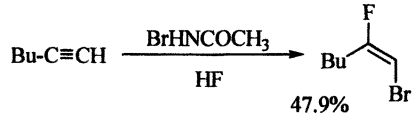
Stereoselective Synthesis of 2-Fluoro-1-haloalkenes (4) and their Derivatives, and their Application to Cross-coupling Reactions

(*E*)-2-Fluoro-1-bromoalkenes (**4b**, X = Br) were stereoselectively prepared by the addition of *in-situ*-generated BrF from *N*-bromoacetamide and HF to 1-alkynes (*25*). Though good stereoselectivity (*E* = 95%) was attained, a drawback was the use of hazardous anhydrous HF as the F source (Scheme 15).



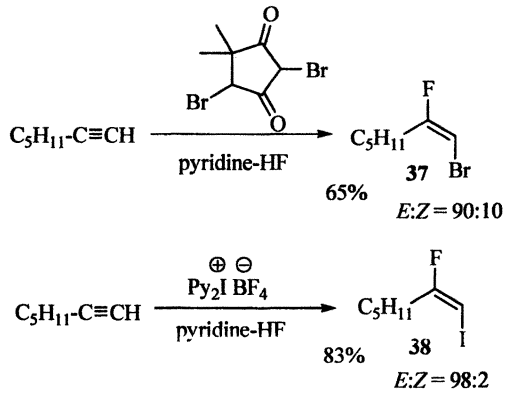


Scheme 14



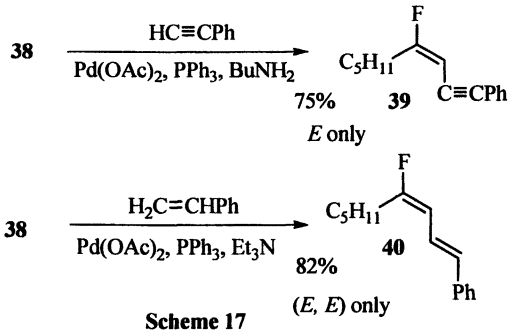
Scheme 15

Rolando *et al.* also synthesized the (*E*)-2-fluoro-1-bromoalkene (**37**) from 1-alkyne using 1,3-dibromo-5,5-dimethylhydantoin as a Br source and pyridine-HF as the F source which is easier to handle than anhydrous HF (*26*). They also synthesized (*E*)-2-fluoro-1-iodoalkene (**38**) with high stereoselectivity (*E* = 98%) from 1-alkyne using bis(pyridine)iodonium tetrafluoroborate and pyridine-HF (*19*) (Scheme 16).



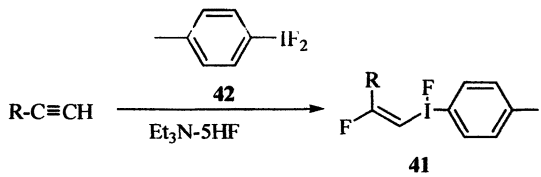
Scheme 16

They used **38** for the Sonogashira reaction and Heck reaction to give (*E*)-2-fluoroenyne (**39**) and (*E,E*)-fluoroalkadiene (**40**) stereoselectively (*19*) (Scheme 17).



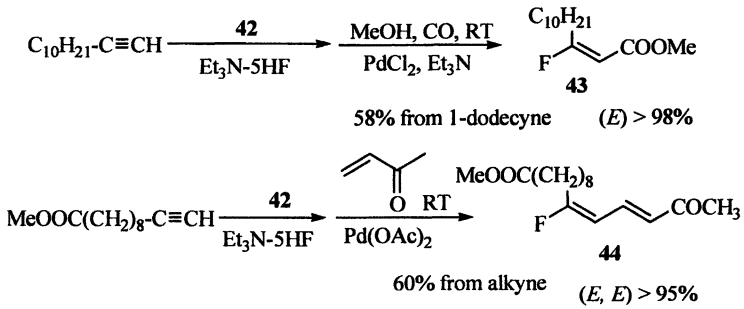
Scheme 17

(*E*)-2-Fluoro-1-alkenyliodonium salts (**41**) could be stereoselectively synthesized by the addition of iodotoluene difluoride (**42**) (*27,28*) to 1-alkynes in the presence of Et_3N-5HF (*29*) (Scheme 18).



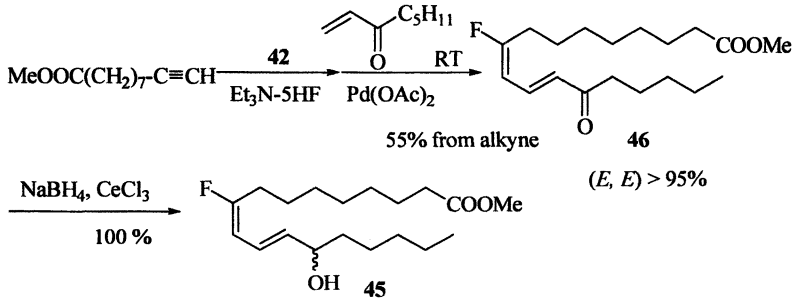
Scheme 18

As the fluoroalkenyliodonium salts **41** are reactive hypervalent compounds, the cross-coupling reaction using **41** proceeds under mild conditions. Methoxycarbonylation reaction and Heck reaction of **41** proceeded at room temperature and the corresponding (*E*)-β-fluoro-α,β-unsaturated ester (**43**) and (*E, E*)-δ-fluoro-α,β,γ,δ-unsaturated carbonyl compounds (**44**) could be stereoselectively obtained, respectively (*30-32*) (Scheme 19).



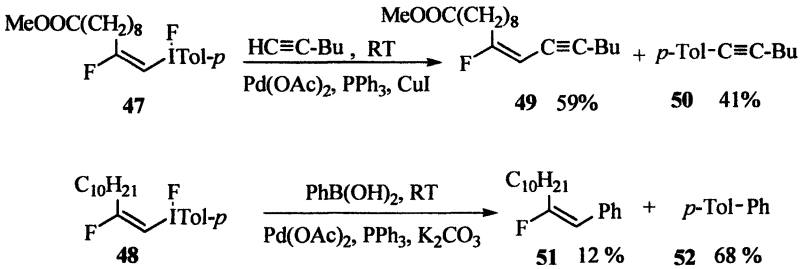
Scheme 19

This methodology was applied for the synthesis of a fluorinated analog (**45**) of a polyunsaturated fatty acid metabolite, (9*Z*, 11*E*)-13-hydroxy-9,11-octadecadienoic acid (coriolic acid) (*33*). Methyl 9-decynoate was converted to the corresponding fluoroalkenyliodonium salt which was used for the Heck reaction with 1-octen-3-one to give methyl (9*E*, 11*E*)-9-fluoro-13-oxooctadecadienoate (**46**). By the reduction of the keto group, the desired **45** could be obtained in racemic form (*31,32*) (Scheme 20).



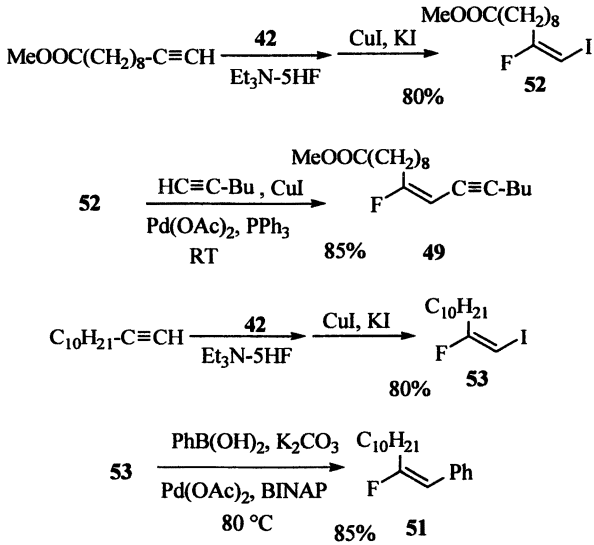
Scheme 20

When (*E*)-2-fluoro-1-alkenyliodonium salts (**47**) and (**48**) were used for the Sonogashira reaction and Suzuki-Miyaura reaction, a significant amount of by-products (**50**) and (**52**) was formed (*34,35*). They were generated by the coupling reaction of alkyne or arylboronic acid with the tolyl group on the iodonium salts. When the fluorine atom was not attached, the cross-coupling reaction took place selectively at the alkenyl part and the arylated by-products were not formed (*36*). Therefore, the fluorine atom on the alkenyl group retarded the oxidative addition of the Pd catalyst and decreased the selectivity (Scheme 21).



Scheme 21

(*E*)-2-Fluoro-1-alkenyliodonium salts **47** and **48** were converted to the corresponding (*E*)-2-fluoro-1-iodoalkenes (**52**) and (**53**) without isolation by Ochiai's method (*37*). Though **52** and **53** are less reactive than **47** and **48**, and higher reaction temperature was required in the Suzuki-Miyaura reactions, the desired (*E*)-fluoroenyne (**49**) and (*E*)-fluoroalkene (**51**) could be obtained selectively (*34,35*) (Scheme 22).

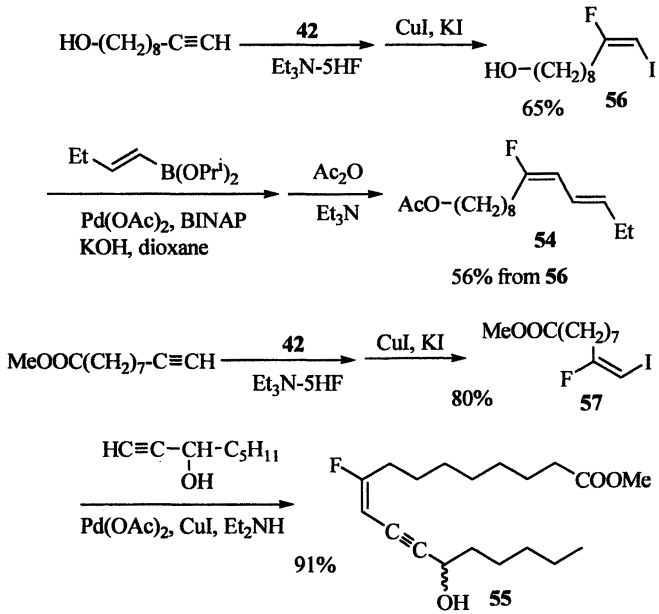


Scheme 22

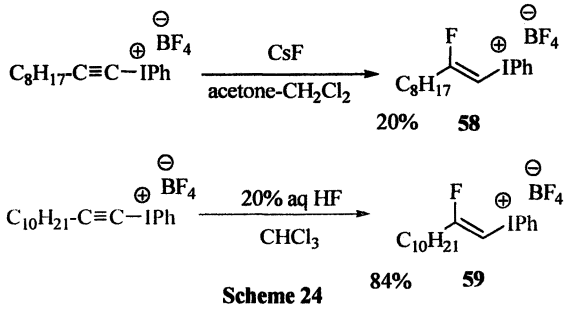
The methodology was applied for the synthesis of fluorinated analogs (**54**) and (**55**) of (9*Z*, 11*E*)-1-acetoxy-9,11-tetradecadiene, a pheromone of the Egyptian cotton leaf worm, and 11,12-dehydrocoriolic acid ester (*38*). 9-Decyn-1-ol was converted to (*E*)-9-fluoro-10-iodo-9-decen-1-ol (**56**) by the reaction with **42**, followed by the treatment of CuI and KI. The cross-coupling reaction of **56** with 1-butenylborane followed by the acetylation of alcohol gave the (9*E*, 11*E*)-1-acetoxy-9-fluoro-9,11-tetradecadiene **54**, the fluorinated analog of the Egyptian cotton leaf worm pheromone (*39*). Racemic 9-fluoro-11,12-dehydrocoriolic acid methyl ester **55** was synthesized by the Sonogashira coupling reaction using fluoroiodoalkene (**57**) prepared from methyl 9-decynoate as shown in Scheme 23 (*34*).

(*Z*)-2-Fluoro-1-alkenyliodonium salts were stereoselectively synthesized by the addition of CsF to 1-alkynyliodonium salts (*40,41*). However, due to the low nucleophilicity and low solubility of the metal fluoride, the yields were low (15 – 20 %). This problem could be overcome by using aq HF as the fluoride source,

and the (*Z*)-2-fluoro-1-alkenylidonium salts could be obtained in good yield with high stereoselectivity (*42*) (Scheme 24).

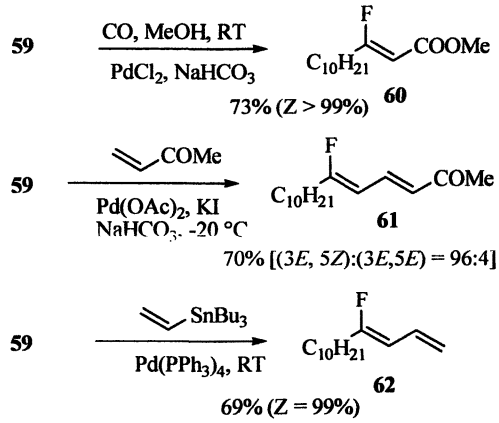


Scheme 23



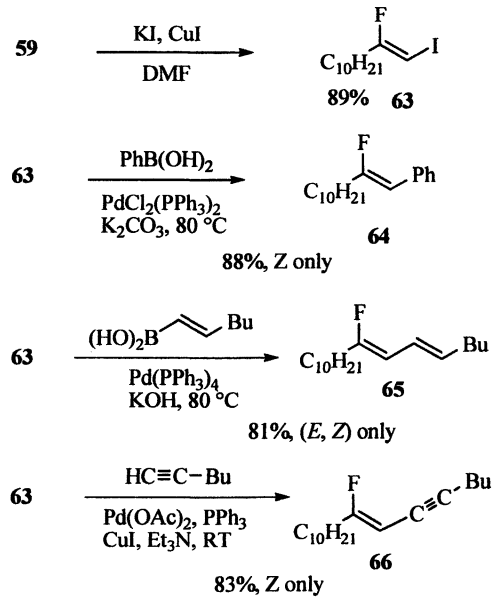
Scheme 24

Application of (*Z*)-2-fluoro-1-alkenylidonium salt **59** for methoxycarbonylation reaction (*43*), Heck reaction (*39*), and Stille reaction (*39*) gave (*Z*)-β-fluoro-α,β-unsaturated ester (**60**), (3*E*, 5*Z*)-δ-fluoro-α,β,γ,δ-unsaturated carbonyl compound (**61**), and (*Z*)-fluoroalkadiene (**62**) stereoselectively (Scheme 25).



Scheme 25

In order to avoid the formation of by-products, **59** was converted to (*Z*)-2-fluoro-1-iodo-1-alkenes (**63**) (*42*), and used for the Suzuki-Miyaura reaction and Sonogashira reaction. From **63**, (*Z*)-fluoroalkene (**64**), (*E, Z*)-fluoroalkadiene (**65**), and (*Z*)-fluoroenyne (**66**) could be obtained stereoselectively (*39*) (Scheme 26).



Scheme 26

Synthesis of 2-Fluoro-1-alkenyl Metals (5)

Though 2-fluoro-1-alkenyl metals (**5**) could be useful precursor for various fluoroalkenes, practical methods for **5** has not been reported yet.

References

(1) Welch, J. T. *Tetrahedron,* **1987**, *43*, 3123-3197.
(2) *Fluorine in Bioorganic Chemistry*; Welch, J. T.; Eswarakrishnan, S.; Wiley, New York, 1991.
(3) *Fluorine-containing Amino Acids*; Kukhar', V. P.; Soloshonok, V. A.; Ed.; Wiley, Chichester, 1994.
(4) Burton, D. J.; Yang, Z.-Y.; Qiu, W. *Chem. Rev.* **1996**, *96*, 1641-1715.
(5) *Metal-catalyzed Cross-coupling Reactions*; Diederich, F.; Stang, P. J. Ed.; Wiley-VCH: Weinheim, 1998.
(6) *Cross-Coupling Reactions;* Miyaura, N.; Ed.; Springer: Berlin, 2002, and references cited.
(7) Shimizu, M.; Yamada, N.; Takebe, Y.; Hata, T.; Kuroboshi, M.; Hiyama, T. *Bull. Chem. Soc. Jpn.*, **1998**, *71*, 2903-2921.
(8) Vanderhaar, R. W.; Burton, D. J.; Naae, D. G. *J. Fluorine Chem.*, **1971**, *1*, 381-383.
(9) Burton, D. J. *J. Fluorine Chem.*, **1983**, *23*, 339-357.
(10) Chen, C.; Wilcoxen, K.; Strack, N.; McCarthy, J. R. *Tetrahedron Lett.*, **1999**, *40*, 827-830.
(11) Eddarir, S.; Francesch, C.; Mestdagh, H.; Rolando, C. *Tetrahedron Lett.*, **1990**, *31*, 4449-4452.
(12) Xu, J.; Burton, D. J. *Tetrahedron Lett.*, **2002**, *43*, 2877-2879.
(13) Chen, C.; Wilcoxen, K.; Huang, C. Q.; Strack, N.; McCarthy, J. R. *J. Fluorine Chem.*, **2000**, *101*, 285-290.
(14) Zhang, X.; Burton, D. J. *J. Fluorine Chem.*, **2001**, *112*, 47-54.
(15) Zhang, X.; Burton, D. J. *J. Fluorine Chem.*, **2001**, *112*, 317-324.
(16) Eddarir, S.; Abdelhadi, Z.; Rolando, C. *Tetrahedron Lett.*, **2001**, *42*, 9127-9130.
(17) Xu, J.; Burton, D. J. *J. Fluorine Chem.*, **2004**, *125*, 725-730.
(18) Xu, J.; Burton, D. J. *Org. Lett.*, **2002**, *4*, 831-833.
(19) Eddarir, S.; Francesch, C.; Mestdagh, H.; Rolando, C. *Bull. Soc. Chim. Fr.*, **1997**, *134*, 741-755.
(20) McCarthy, J. R.; Huber, E. W.; Le, T.-B.; Laskovics, F. M.; Matthews, D. P. *Tetrahedron*, **1996**, *52*, 45-58.
(21) Chen, C.; Wilcoxen, K.; Kim, K.; McCarthy, J. R. *Tetrahedron Lett.*, **1997**, *38*, 7677-7680.

(22) Chen, C.; Wilcoxen, K.; Zhu, Y.-F.; Kim, K.; McCarthy, J. R. *J. Org. Chem.*, **1999**, *64*, 3476-3482.
(23) Xu, J.; Burton, D. J. *Tetrahedron Lett.*, **2002**, *43*, 4565-4567.
(24) Eddarir, S.; Rolando, C. *J. Fluorine Chem.*, **2004**, *125*, 377-380.
(25) Dear, R. E. A. *J. Org. Chem.*, **1970**, *35*, 1703-1705.
(26) Eddarir, S.; Mestdagh, H.; Rolando, C. *Tetrahedron Lett.*, **1991**, *32*, 69-72.
(27) Carpenter, W. *J. Org. Chem.*, **1966**, *31*, 2688-2689.
(28) Sawaguchi, M.; Ayuba, S.; Hara, S. *Synthesis*, **2002**, 1802-1803.
(29) Hara, S.; Yoshida, M.; Fukuhara, T.; Yoneda, N. *Chem. Commun.*, **1998**, 965-966.
(30) Hara, S.; Yamamoto, K.; Yoshida, M.; Fukuhara, T.; Yoneda, N. *Tetrahedron Lett.*, **1999**, *40*, 7815-7818.
(31) Yoshida, M.; Hara, S.; Fukuhara, T.; Yoneda, N. *Tetrahedron Lett.*, **2000**, *41*, 3887-3890.
(32) Yoshida, M.; Nagahara, D.; Fukuhara, T.; Yoneda, N.; Hara, S. *J. Chem. Soc., Perkin Trans. 1*, **2001**, 2283-2288.
(33) Kato, T.; Yamaguchi, Y.; Hirano, T.; Yokoyama, T.; Uyehara, T.; Namai, T.; Yamanaka, S.; Harada, N. *Chem. Lett.*, **1984**, 409-412.
(34) Yoshida, M.; Yoshikawa, S.; Fukuhara, T.; Yoneda, N.; Hara, S. *Tetrahedron*, **2001**, *57*, 7143-7148.
(35) Yoshida, M.; Ota, D.; Fukuhara, T.; Yoneda, N.; Hara, S. *J. Chem. Soc., Perkin Trans. 1*, **2002**, 384-389.
(36) Kang, S.-K.; Lee, H.-W.; Jang, S.-B.; Ho, P.-S. *J. Org. Chem.*, **1996**, *61*, 4720-4724.
(37) Ochiai, M.; Sumi, K.; Takaoka, Y.; Kunishima, M.; Nagao, Y.; Shiro, M.; Fujita, E. *Tetrahedron*, **1988**, *44*, 4095-4112.
(38) Kobayashi, Y.; Okamoto, S.; Shimazaki, T.; Ochiai, Y.; Sato, F. *Tetrahedron Lett.*, **1987**, *28*, 3959-3962.
(39) Yoshida, M. Dissertation, HokkaidoUniversity, 2004.
(40) Ochiai, M.; Oshima, K.; Masaki, Y. *Chem. Lett.*, **1994**, 871-874.
(41) Ochiai, M.; Kitagawa, Y.; Toyonari, M.; Uemura, K.; Oshima, K.; Shiro, M. *J. Org. Chem.*, **1997**, *62*, 8001-8008.
(42) Yoshida, M.; Hara, S. *Org. Lett.*, **2003**, *5*, 573-574.
(43) Yoshida, M.; Komata, A.; Hara, S. *J. Fluorine Chem.*, **2004**, *125*, 527-529.