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Author(s)	YOSHIDA, Masanori
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Stereoselective Synthesis of Fluoroalkenes Using Fluoroalkenylodonium Salts

A Thesis

Submitted to Graduate School of Engineering, Hokkaido University

for the Degree of Doctor of Engineering

by

Masanori YOSHIDA

2004

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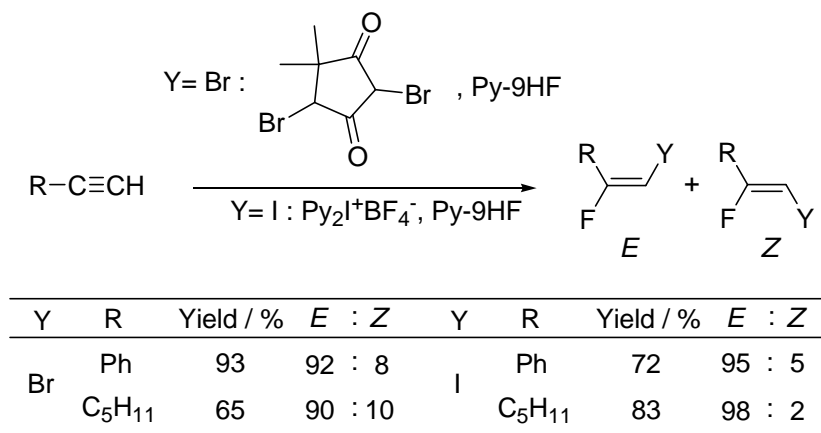
Introduction

Introduction of a fluorine atom into a biologically active compound has received considerable attention of biological and medicinal chemists, since the fluorine atom can dramatically enhance the biological activity.¹ In a synthesis of a biologically active compound bearing a fluoroalkene moiety, the regio- and stereoselective introduction of the fluorine atom is important because the bioactivity strongly depends on the position and stereochemistry of the fluorine atom.² Therefore, much effort has been made for development of a regio- and stereoselective synthesis of fluoroalkenes.^{3,4,5} The most popular approach to the stereoselective synthesis of fluoroalkenes is via the Horner-Wadsworth-Emmons reaction using fluorine containing organophosphonate.⁴ However, in this methodology, a mixture of (*E*)- and (*Z*)-isomers generally formed. Recently, Mestdagh *et al.* reported the stereoselective synthesis of (*E*)-1-bromo-2-fluoroalk-1-enes and (*E*)-2-fluoro-1-iodoalk-1-enes by the halofluorination of alk-1-yne using pyridinium poly(hydrogen fluoride) and 1,3-dibromo-5,5-dimethylhydantoin or iododipyridinium tetrafluoroborate (Scheme 1).⁵ However, they prepared the (*E*)-2-fluoro-1-haloalkenes from only two simple substrates, hept-1-yne and phenylacetylene. Furthermore, they have been able to synthesize the (*E*)-isomer of 2-fluoro-1-haloalk-1-ene, but the stereoselective synthesis of the corresponding (*Z*)-isomer is still difficult.

Horner-Wadsworth-Emmons reaction



Halofluorination of alk-1-yne

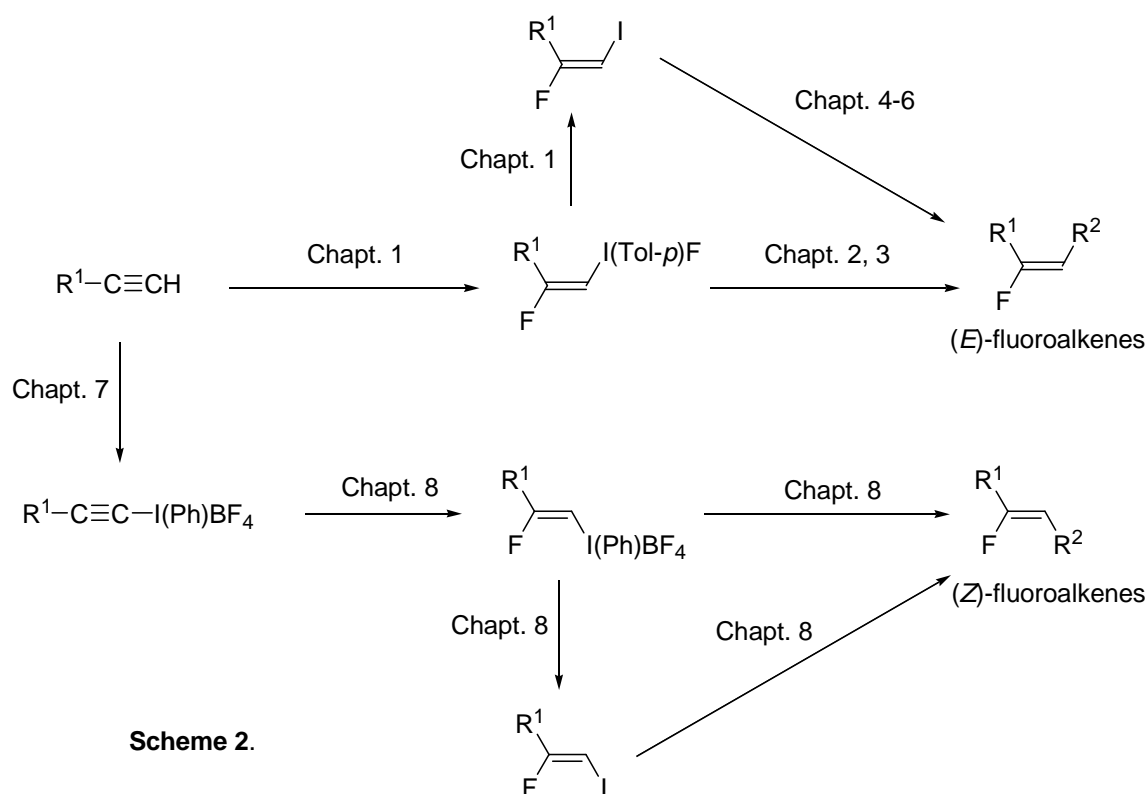


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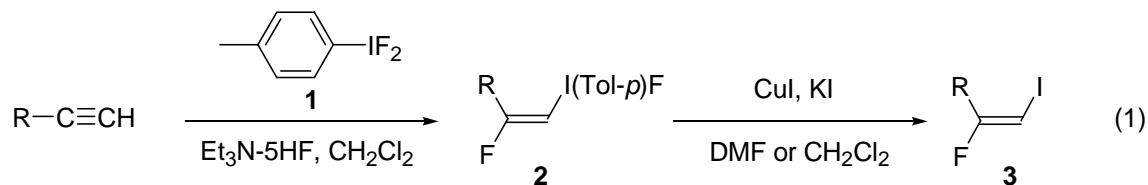
Scheme 1.

The author developed a highly stereoselective synthesis of (*E*)-2-fluoroalk-1-enyliodonium salts and their application to the stereoselective synthesis of (*E*)-2-fluoroalk-1-ene derivatives by Pd-catalyzed coupling reactions. Efficient methodologies for the synthesis of alkynyliodonium salts and for their transformation to (*Z*)-2-fluoroalk-1-enyliodonium salts were also developed. A variety of (*Z*)-2-fluoroalk-1-ene derivatives were stereoselectively synthesized via Pd-catalyzed coupling reactions using the (*Z*)-fluoroalkenyliodonium salts.

The synthetic pathways of (*E*)- and (*Z*)-2-fluoroalk-1-ene derivatives described in this thesis are summarized in Scheme 2.

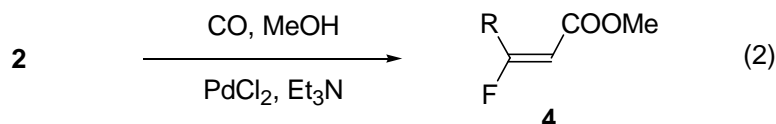


In Chapter 1, stereoselective synthesis of (*E*)-2-fluoro-1-iodoalk-1-enes (**3**)⁵ from terminal alkynes is described. The author found *p*-iodotoluene difluoride⁶ (**1**) regio- and stereoselectively adds to terminal alkynes in the presence of triethylamine pentakis hydrogen fluoride ($\text{Et}_3\text{N}\cdot 5\text{HF}$)⁷ to give (*E*)-2-fluoroalk-1-enyl(4-methylphenyl)iodonium fluorides (**2**). (*E*)-2-Fluoro-1-iodoalkenes (**3**) were stereoselectively prepared by the treatment of **2** with CuI and KI ($E/Z \geq 98/2$) [Eq. (1)].

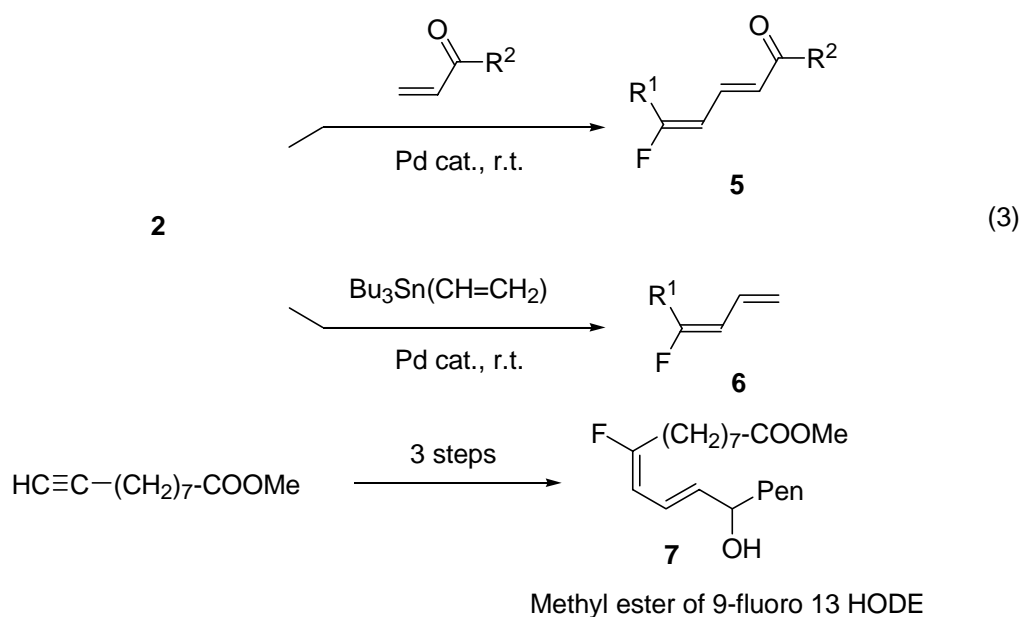


In Chapter 2, stereoselective synthesis of (*E*)- β -fluoro- α,β -unsaturated esters (**4**) is described. Though α -fluoro- α,β -unsaturated esters³ are readily obtained by the Horner-Wadsworth-Emmons reaction, the stereoselective synthesis of β -fluoro- α,β -unsaturated esters has not

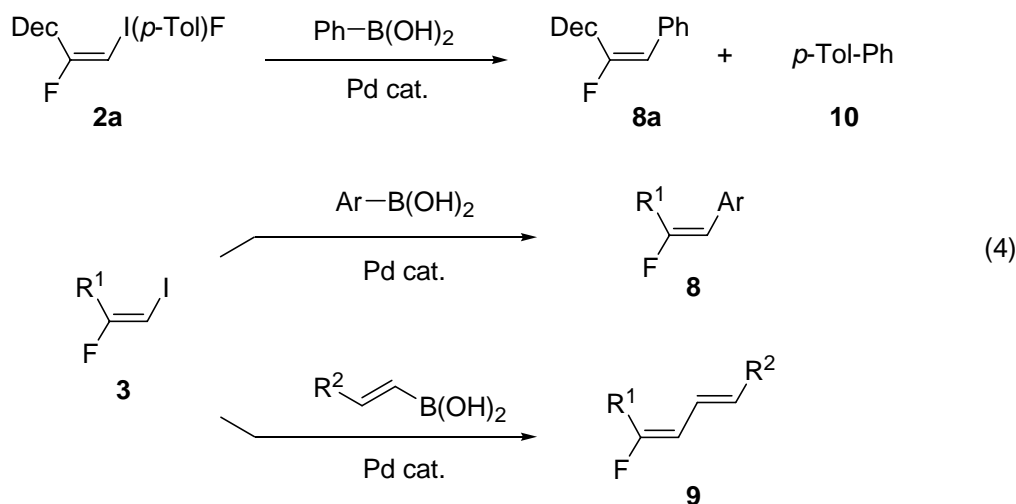
been reported. The author succeeded in obtaining (*E*)- β -fluoro- α,β -unsaturated esters (**4**) stereoselectively in good yields by carbomethoxylation¹² of (*E*)-2-fluoroalkenyliodonium salts (**2**) prepared in Chapter 1 [Eq. (2)].



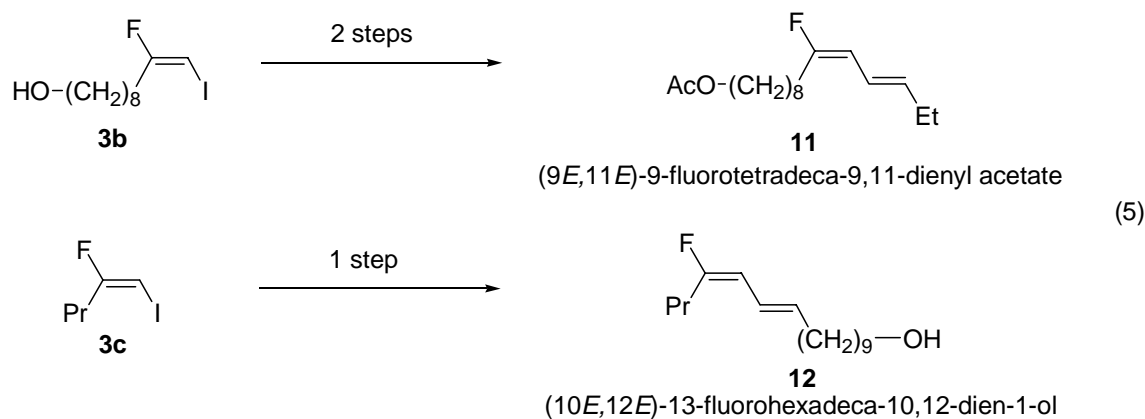
In Chapter 3, stereoselective synthesis of fluoroalkadienes using (*E*)-2-fluoroalkenyliodonium salts (**2**) is described. The Pd-catalyzed cross-coupling reactions of organic halides with olefins and organostannanes are known as the Heck reaction⁸ and the Stille reaction,⁹ respectively. The author found the Heck reaction of **2** with α,β -unsaturated carbonyl compounds readily proceeded under mild conditions to give various (*E*)- δ -fluoro- $\alpha,\beta,\gamma,\delta$ -unsaturated carbonyl compounds (**5**) in good yields [Eq. (3)]. This methodology was applicable to the synthesis of methyl (9*E*,11*E*)-9-fluoro-13-hydroxy-octadeca-9,11-dienoate (**7**) which is the fluorinated analogue of a natural product having inhibitory activity against rice blast fungus. Moreover, the author succeeded in synthesizing a variety of (*E*)-4-fluoroalka-1,3-dienes (**6**) by the Stille coupling reaction of **2** with tributylvinylstannane.



In Chapter 4, stereoselective synthesis of fluoroalkenes using (*E*)-2-fluoroalkenyliodonium salts (**2**) or (*E*)-2-fluoro-1-iodoalkenes (**3**) with organoboranes is described. The Pd-catalyzed cross-coupling reaction of organic halides with organoboranes is known as the Suzuki-Miyaura coupling reaction.¹⁰ The coupling reaction of (*E*)-2-fluorododecenyliodonium salt (**2a**) with phenylboronic acid smoothly proceeded under mild conditions; however, a mixture of (*E*)-2-fluoro-1-phenyldodec-1-ene (**8a**) and 4-phenyltoluene (**10**), generated by the coupling reaction between the tolyl group of **2a** and phenylboronic acid, was obtained [Eq. (4)]. The iodonium salt (**2a**) was converted to (*E*)-2-fluoro-1-iodododec-1-ene (**3a**), and then, it was subjected to the Suzuki-Miyaura coupling to give **8a**. By this method, the author succeeded in obtaining fluoroalkenes (**8**) stereoselectively in good yields from various arylboranes and **3**. A variety of fluoroalkadienes (**9**) were also synthesized by the coupling reaction of **3** with alkenylboranes.

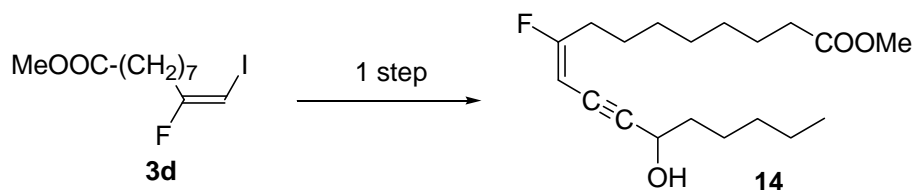
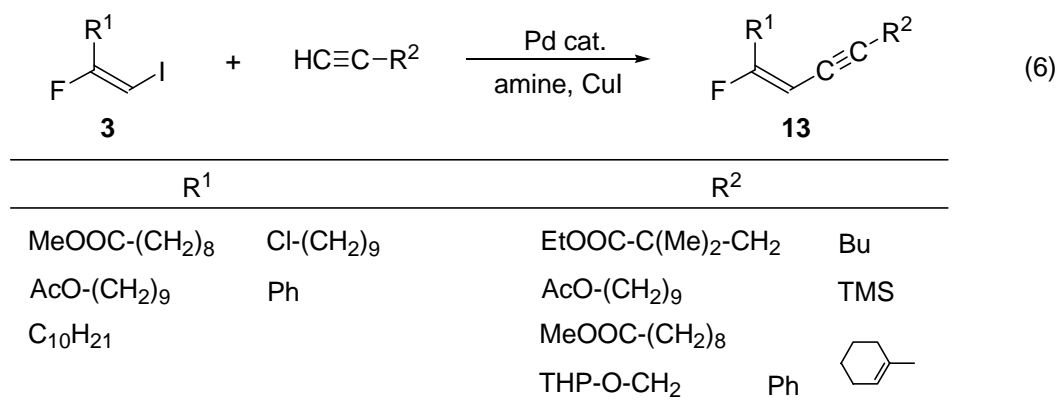


In Chapter 5, the cross-coupling reaction using (*E*)-2-fluoro-1-iodoalkenes (**3**) with organoboranes was applied to synthesize the fluorinated analogues of natural compounds. Two fluorinated analogues of insect sex pheromones having a diene moiety (**11** and **12**) were synthesized [Eq. (5)].

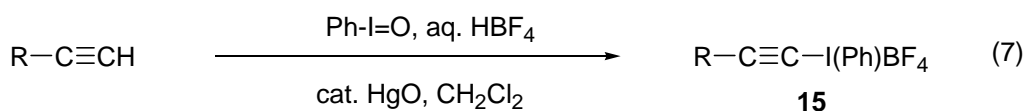


In Chapter 6, stereoselective synthesis of (*E*)-1-fluoro-1,3-enynes (**13**) is described. The Pd-catalyzed cross-coupling reaction using organic halides with alk-1-ynes in the presence of CuI is known as the Sonogashira coupling reaction.¹¹ Mestdagh *et al.* previously reported the stereoselective synthesis of fluoroenynes (**13**); however, they presented the coupling reaction of only two simple substrates, (*E*)-2-fluoro-1-iodo-2-phenylethene and (*E*)-2-fluoro-1-iodohept-1-ene, with phenylacetylene.⁵

The author prepared 5 examples of (*E*)-2-fluoro-1-iodoalk-1-enes and converted them to 15 examples of fluoroenynes (**13**) having various functional groups by the Sonogashira reaction [Eq. (6)]. (*E*)-9-Fluoro-11,12-dehydrocoriolic acid methyl ester (**14**), a fluorinated analogue of polyfunctionalized biologically active compound, was also synthesized by this method.



In Chapter 7, a direct synthesis of alk-1-ynyl(phenyl)iodonium salts¹³ (**15**) from alk-1-ynes is described. Alkynyliodonium salts (**15**) are highly reactive in Michael-type conjugate addition reactions because of the strong electron-withdrawing property of the iodonium group. Therefore, they reacted with various nucleophiles to give (*Z*)- β -functionalized alkenyliodonium salts. (*Z*)-2-Fluoroalk-1-enyliodonium salts have been synthesized by this method (Chapter 8 deals with this reaction). Alkynyliodonium salts (**15**) are generally synthesized from alk-1-ynes in two steps through the corresponding alkynylsilanes or -stannanes. The author found alkynyliodonium salts (**15**) had been directly obtained from alk-1-ynes in good yields by the reaction with iodosylbenzene in the presence of aq. HBF₄ and a catalytic amount of HgO [Eq. (7)].



In Chapter 8, stereoselective synthesis of (*Z*)-2-fluoroalk-1-enyliodonium salts (**16**) and their application to the syntheses of (*Z*)-2-fluoroalk-1-ene derivatives (**17**) is described. Ochiai *et al.* previously reported the Michael-type addition of a fluoride anion to alkynyliodonium salts (**15**) gave (*Z*)-fluoroalkenyliodonium salts (**16**); however, the yields were low (15-20%).¹⁴ The author found that alkynyliodonium salts (**15**) were converted to (*Z*)-fluoroalkenyliodonium salts (**16**) in moderate to good yields (43-84%) by the reaction with hydrofluoric acid. By Pd-catalyzed coupling reactions using **16**, the author succeeded in obtaining a variety of (*Z*)-2-fluoroalk-1-ene derivatives (**17**) [Eq. (8)].



Thus, the author succeeded in synthesizing a variety of (*E*)- and (*Z*)-fluoroalkenes stereoselectively by Pd-catalyzed cross-coupling reactions using fluoroalkenyliodonium salts.

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Chapter 1

Selective Synthesis of (*E*)-2-Fluoro-1-iodoalk-1-enes from Alk-1-yne via (*E*)-2-Fluoroalk-1-enyliodonium Salts

Abstract

p-Iodotoluene difluoride reacted with terminal alkynes in the presence of Et₃N·5HF to give (*E*)-2-fluoroalk-1-enyl(4-methylphenyl)iodonium fluorides which could be converted to (*E*)-2-fluoro-1-iodoalk-1-enes in 55-80% yield from the alkynes. The reaction can be carried out without the protection of functional groups, e.g., a ketone, ester or hydroxyl group.

Introduction

The introduction of a fluorine atom into the double bond of natural products, such as terpenes,¹ nucleosides,² retinal,³ fatty acids,⁴ prostaglandins⁵ and peptides⁶ has been of great interest because the fluorinated analogues of natural compounds are expected to have different pharmacological properties from the original compounds (Figure 1).

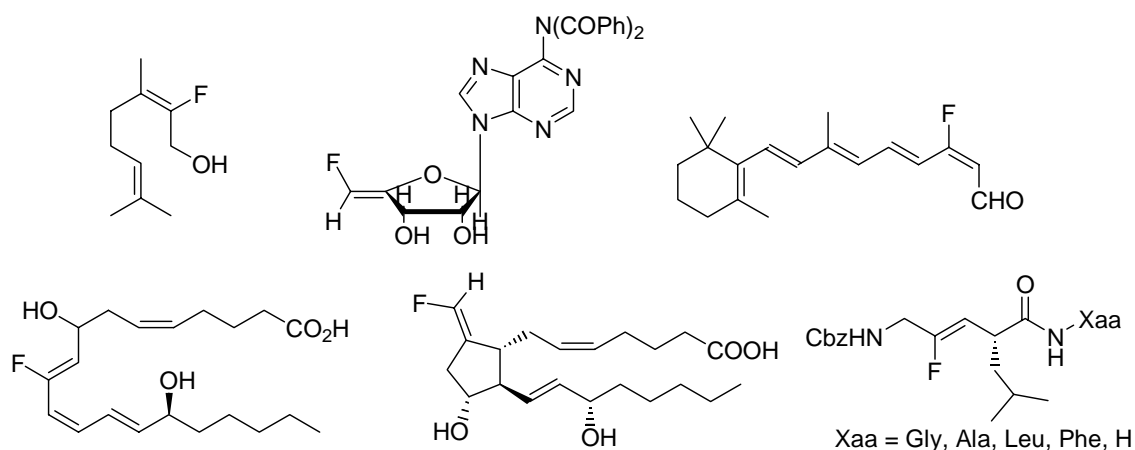
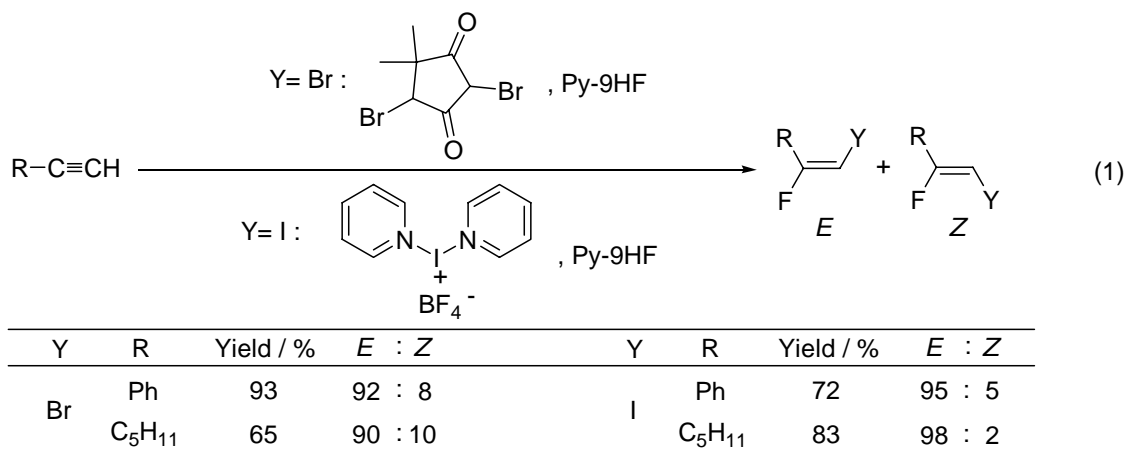


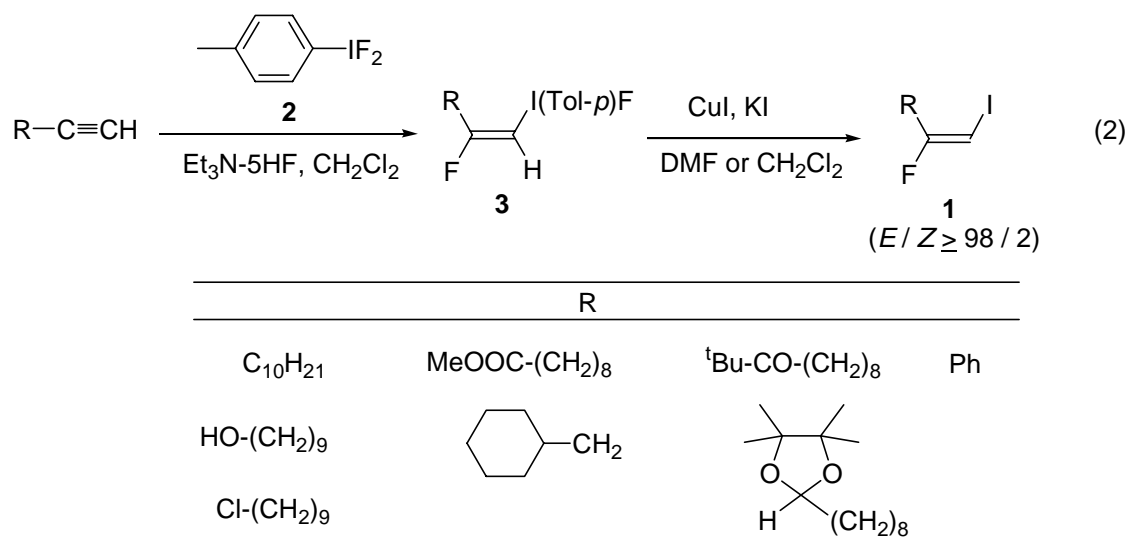
Figure 1.

The most popular approach to synthesizing the fluoroalkenyl parts of such compounds is via the Horner-Wadsworth-Emmons reaction using fluorine containing organophosphonate with carbonyl compound, although a mixture of stereoisomers generally formed.²⁻⁷ A cross-coupling reaction using fluoroalkenyl halides or metals would be a versatile method for the stereoselective synthesis of fluoroalkenes.⁸ However, the cross-coupling method has not been adequately developed because stereoselective synthesis of the fluoroalkenyl halides or metals is difficult. Recently, Mestdagh *et al.* reported the bromofluorination of terminal alkynes with 1,3-dibromo-5,5-dimethylhydantoin (DBH) and pyridinium poly(hydrogen fluoride) to give (*E*)-1-bromo-2-fluoroalk-1-enes with good stereoselectivity (*E* / *Z* \geq 90 / 10).⁹ The iodofluorination of terminal alkynes was also performed using bis(pyridine)iodonium tetrafluoroborate and pyridinium

poly(hydrogen fluoride) to afford (*E*)-2-fluoro-1-iodoalk-1-enes (**1**) (*E* / *Z* \geq 95 / 5) [Eq. (1)]. However, they presented these halofluorination reactions using only two simple substrates, phenyl acetylene and heptyne. For application to the fluorinated analogues of natural compounds, the synthesis of polyfunctionalized substrates is required.



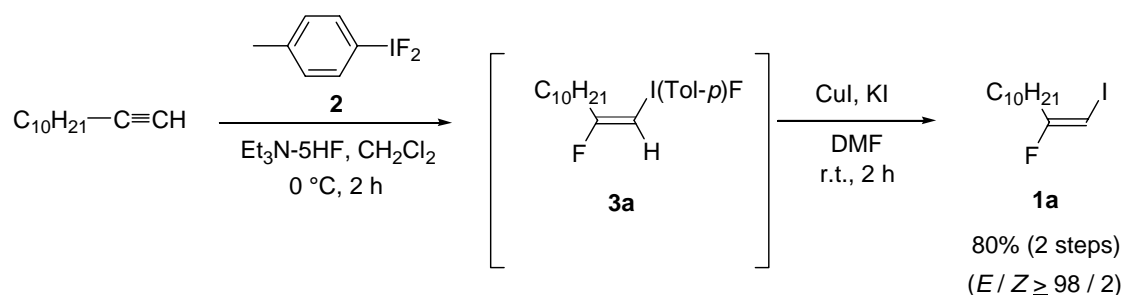
The author found the reaction of terminal alkynes with *p*-iodotoluene difluoride (**2**), which is known as a stable and mild fluorinating reagent,¹⁰ in the presence of triethylamine pentakis hydrogen fluoride (Et₃N-5HF)¹¹ gave (*E*)-2-fluoroalk-1-enyl(4-methylphenyl)iodonium fluorides (**3**) stereoselectively (*E* / *Z* \geq 98 / 2) [Eq. (2)].^{12,13} It was previously shown by Ochiai *et al.* that the hypervalent iodine group of alkenyliodonium salts was successfully substituted by iodine with CuI and KI.¹⁴ By using this method, the author attempted to convert the fluoroalkenyliodonium salts (**3**) to the corresponding fluoroiodoalkenes (**1**). As expected, the transformation of **3** to **1** smoothly proceeded in 55-80% yields from alk-1-yne with high stereoselectivity (*E* / *Z* \geq 98 / 2). Since these reactions can be carried out without the protection of functional groups, such as a ketone, ester or hydroxyl group, a variety of (*E*)-fluoroiodoalkenes (**1**) were readily obtained from alk-1-yne.



The details of the synthesis of fluoriodoalkenes (**1**) from alk-1-ynes will be shown in this chapter.

Results and Discussion

p-Iodotoluene difluoride (**2**) was electrochemically prepared from *p*-iodotoluene in Et₃N–5HF.¹⁵ This Et₃N–5HF solution of **2** was added to a dichloromethane solution of dodec-1-yne at 0 °C. After the reaction mixture was stirred for 2 h at 0 °C, (*E*)-2-fluorododec-1-enyl(4-methylphenyl)iodonium fluoride (**3a**) was generated.¹⁶ Then it was attempted to convert **3a** into (*E*)-2-fluoro-1-iodododec-1-ene (**1a**) with 1 eq. of CuI and KI to dodecyne in DMF according to Ochiai's method.¹⁴ Conveniently, the isolation of **3a** had not been required for the iodination reaction, and **1a** was obtained in 80% isolated yield based on dodec-1-yne used (Scheme 1).



Scheme 1. Synthesis of (*E*)-2-fluoro-1-iodododec-1-ene (**1a**)

The stereochemistry of **1a** was determined by ¹H NMR (Figure 2). A vinylic hydrogen signal was observed at 5.63 ppm with a 17.7 Hz coupling constant which was in good agreement with the reported data of (*E*)-2-fluoro-1-iodohept-1-ene.⁹ Therefore, the stereochemistry of the hydrogen and fluorine on the double bond was determined as *cis*-configuration. The stereoselectivity was determined by GC analysis, ¹H NMR and ¹⁹F NMR spectrum of **1a** (*E* / *Z* ≥ 98 / 2).

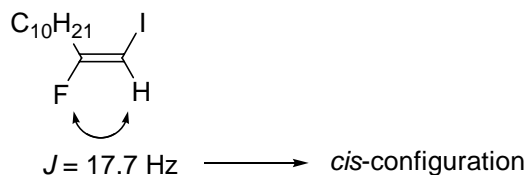
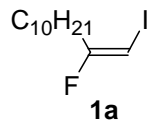
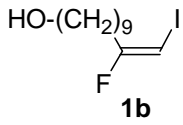
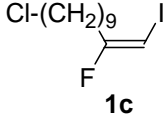
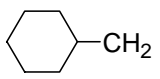
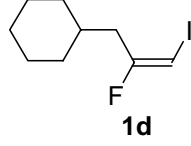
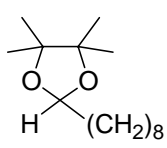
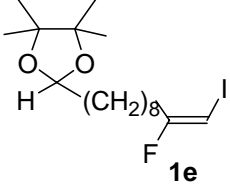
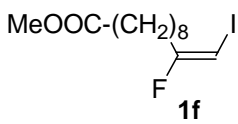
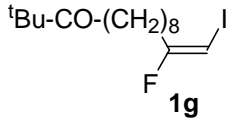
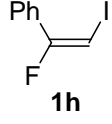


Figure 2.

(*E*)-2-Fluoro-1-iodoalk-1-enes (**1**) having a variety of functionalities were synthesized in a similar manner (Table 1). The reaction conditions for the preparation of **1** from the corresponding fluoroalkenyliodonium salts (**3**) should be modified according to their functionalities. When the reaction mixture of fluoroalkenyliodonium salt (**3b**) prepared from 11-hydroxyundec-1-yne was treated under the same conditions for the preparation of **1a**, (*E*)-10-fluoro-11-iodoundec-10-en-1-ol (**1b**) was obtained in 56% yield from the alkyne (Method *A*, Entry 2). When the iodination reaction of **3b** was carried out with 10 eq. of CuI and KI to the alkyne in dichloromethane, **1b** was obtained in 65% yield (Method *B*, Entry 3). Similarly, 11-chloroundec-1-yne and 3-cyclohexylprop-1-yne were converted to the corresponding fluoroiodoalkenes (**1c-d**) by Method *B* (Entries 4 and 5). In the case of alkyne bearing an acetal group, it was required to remove Et₃N·5HF after the preparation of fluoroalkenyliodonium salt (**3e**). The following iodination with 10 eq. of CuI and KI to the alkyne in dichloromethane smoothly proceeded to give the corresponding fluoroiodoalkene (**1e**) in 55% yield from the alkyne (Method *C*, Entry 8). Methyl undec-10-ynoate and 2,2-dimethyltridec-12-yn-3-one were also transformed into the fluoroiodoalkenes (**1f,g**) in good yields by Method *C* (Entries 9 and 10). Phenylacetylene could be converted to (*E*)-2-fluoro-2-phenyl-1-iodoethene (**1h**); however, the corresponding fluoroalkenyliodonium salt (**3h**) was unstable under these reaction conditions, and it caused the low yield of **1h** (36%, Entry 11).

Table 1. Syntheses of (*E*)-2-fluoro-1-iodoalk-1-enes^a

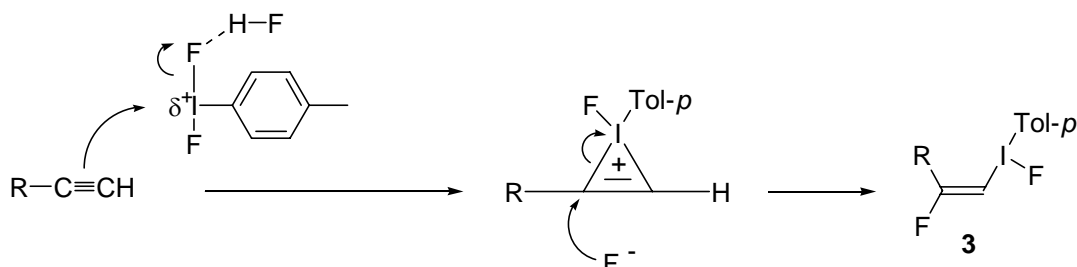
Entry	R	Time 1 / h	Method	Time 2 / h	Yield of 1 / % ^b	Product
1	C ₁₀ H ₂₁ (3a)	2	A	2	80	
2	HO-(CH ₂) ₉ (3b)	8	A	36	56	
3		8	B	72	65	
4	Cl-(CH ₂) ₉ (3c)	8	B	72	77	
5	 (b) (3d)	12	B	72	65	
6	 (3e)	14	A	2	46	
7		14	B	72	47	
8		14	C	72	55	
9	MeOOC-(CH ₂) ₈ (3f)	8	C	72	80	
10	^t Bu-CO-(CH ₂) ₈ (3g)	14	C	72	72	
11	Ph (3h)	2	A	12	36	
12		2	C	72	0	

^a Method: A; After the reaction of alkyne (2 mmol) with **2**, 1 eq. of CuI and KI in DMF (2 mL) was added. B; After the reaction of alkyne (2 mmol) with **2**, the reaction mixture was added to a mixture of 10 eq. of CuI and KI in CH₂Cl₂ (30 mL). C; After the reaction of alkyne (2 mmol) with **2**, Et₃N-5HF was removed and the residue containing **3** was dissolved in CH₂Cl₂ (5 mL). Then the CH₂Cl₂ solution of **3** was added to a mixture of 10 eq. of CuI and KI in CH₂Cl₂ (25 mL).

^b Isolated yield based on alkyne used.

Reaction mechanism

In the addition reaction of iodotoluene difluoride (**2**) to the triple bond, $\text{Et}_3\text{N}\cdot 5\text{HF}$ played an important role because **3a** could not be obtained in the absence of $\text{Et}_3\text{N}\cdot 5\text{HF}$ or in the presence of lower acidic $\text{Et}_3\text{N}\cdot n\text{HF}$, such as $\text{Et}_3\text{N}\cdot 4\text{HF}$ and $\text{Et}_3\text{N}\cdot 3\text{HF}$, instead of $\text{Et}_3\text{N}\cdot 5\text{HF}$. A possible mechanism of the addition of **2** to dodec-1-yne is illustrated in Scheme 2. Iodotoluene difluoride (**2**) was activated by a hydrogen fluoride derived from $\text{Et}_3\text{N}\cdot 5\text{HF}$. The electron pair from the triple bond of dodec-1-yne attacked the polarized iodine to give an iodonium ion intermediate. In the next step, the fluoride anion attacked this intermediate according to the Markovnikov rule from the unshielded side to produce (*E*)-2-fluorododec-1-enyl(4-methylphenyl)iodonium fluoride (**3a**).¹² The reaction mechanism is similar to that of an addition of bromine to alkynes. The mechanism of transformation from alkenyliodonium salts to iodoalkenes was well investigated by Ochiai *et al.*¹⁴



Scheme 2. A possible mechanism of the addition of iodotoluene difluoride to terminal alkynes.

Conclusion

Highly stereoselective synthesis of (*E*)-2-fluoro-1-iodoalk-1-enes was accomplished by the addition of *p*-iodotoluene difluoride to alk-1-ynes in the presence of Et₃N·5HF, followed by the treatment of CuI and KI. (*E*)-2-Fluoro-1-iodoalk-1-enes having a variety of functionalities were synthesized in good yields without the protection of functionalities such as ketones, esters or even hydroxyl groups.

Experimental

General

The IR spectra were recorded using a JASCO FT/IR-410. The ^1H NMR (400 MHz) and ^{19}F NMR (376 MHz) spectra were recorded in CDCl_3 on a JEOL JNM-A400II FT NMR and the chemical shifts, δ , are referred to TMS (^1H) and CFCl_3 (^{19}F), respectively. The EI-low and high-resolution mass spectra were measured on a JEOL JMS-700TZ, JMS-FABmate or JMS-HX110. For column chromatography, Merck silica gel 7734 was used and for analytical thin layer chromatography, Merck silica gel 5715 was used. The $\text{Et}_3\text{N}\cdot 5\text{HF}$ was prepared by the addition of freshly distilled Et_3N to anhydrous HF at 0 °C as reported before.¹⁷ Dodec-1-yne,^{18c} undec-10-yn-1-ol^{18a} and 3-cyclohexylprop-1-yne^{18a} was prepared according to the literature. Methyl undec-10-ynoate was obtained by esterification of undec-10-ynoic acid^{18b} prepared from undec-10-enoic acid. Undec-10-enoic acid and phenylacetylene were purchased from Tokyo Kasei Co., Ltd., and used without further purification. 11-Chlorododec-1-yne^{18a} was prepared from undec-10-yn-1-ol.

Preparation of 2,2-dimethyltridec-12-yn-3-one

To a dry Et_2O solution (50 mL) of $^t\text{BuMgBr}$ (40 mmol) was slowly added a dry Et_2O solution (30 mL) of undec-10-yn-1-al prepared by the PCC oxidation of undec-10-yn-1-ol¹⁹ (4.98g, 30 mmol) at room temperature. After stirring the reaction mixture for 3 h under reflux, the reaction mixture was cooled to 0 °C. Then the reaction mixture was poured into 25% aq. NH_4Cl (50 mL), and the organic phase was separated. The aqueous phase was extracted with Et_2O (30 mL \times 3). The combined organic phase was dried over MgSO_4 and solvent was removed under reduced pressure. The obtained crude 2,2-dimethyltridec-12-yn-3-ol was used further PCC oxidation. After the purification by column chromatography (silica gel/hexane), 2,2-dimethyltridec-12-yn-3-one was

obtained in 34% yield from undec-10-yn-1-al.

Preparation of 2-(dec-9-ynyl)-4,4,5,5-tetramethyl-[1,3]dioxolane

In a flask equipped with a Dean-Stark trap were placed undec-10-yn-1-al (3.32g, 20 mmol), pinacol (7.67g, 65 mmol), *p*-toluene sulfonic acid monohydrate (0.38g, 2 mmol) and benzene (50 mL). After stirring under reflux for 16 h, the reaction mixture was poured into water (50 mL) and extracted with Et₂O (30 mL × 3). The combined organic phase was successively washed with water (100 mL), saturated aq. NaHCO₃ (100 mL) and brine (100 mL). The ethereal solution was dried over MgSO₄ and solvent was removed under reduced pressure to give 2-(dec-9-ynyl)-4,4,5,5-tetramethyl-[1,3]dioxolane in 98% yield from undec-10-yn-1-al.

Synthesis of *p*-iodotoluene difluoride

p-Iodotoluene difluoride was electrochemically prepared in a divided cell made of Teflon™ PFA with a Nafion™ 117 film using two smooth Pt sheets (20 × 20 mm) for the anode and cathode. *p*-Iodotoluene (3 mmol) and Et₃N–5HF (22 mL) were introduced into the anodic cell and Et₃N–5HF (22 mL) was introduced into the cathodic cell. The electrolysis was carried out under constant electricity (50 mAh⁻¹) until 2 F mol⁻¹ of electricity was passed. The resulting Et₃N–5HF solution of *p*-iodotoluene difluoride in the anodic cell was used for further reaction.

Synthesis of (*E*)-2-fluoro-1-iodoalk-1-ene (3) with method A

Typical experimental procedure: Dodec-1-yne (332 mg, 2 mmol) and CH₂Cl₂ (6 mL) were introduced into a reaction vessel made of Teflon™ PFA and *p*-iodotoluene difluoride (3 mmol) in Et₃N–5HF (22 mL) was added at 0 °C. After stirring for 2 h at 0 °C, a mixture of CuI (380 mg, 2 mmol) and KI (332 mg, 2 mmol) in DMF (2 mL) was added. The resulting reaction mixture was stirred at room temperature for 2 h and then solid was removed by filtration through Celite. The obtained filtrate was poured

into water (30 mL) and extracted with CH₂Cl₂ (20 mL × 3). The combined organic phase was dried over MgSO₄ and solvent was removed under reduced pressure. The product was isolated by column chromatography (silica gel/hexane) in 80% yield.

Synthesis of (*E*)-2-fluoro-1-iodoalk-1-ene (3) with method B

Typical experimental procedure: 11-Chloroundec-1-yne (371 mg, 2 mmol) and CH₂Cl₂ (6 mL) were introduced into a reaction vessel made of Teflon™ PFA and *p*-iodotoluene difluoride (3 mmol) in Et₃N–5HF (22 mL) was added at 0 °C. After stirring for 8 h at 0 °C, the reaction mixture was added to a mixture of CuI (3.8 g, 20 mmol) and KI (3.32 g, 20 mmol) in CH₂Cl₂ (30 mL). The resulting reaction mixture was stirred at room temperature for 72 h and then solid was removed by filtration through Celite. The obtained filtrate was poured into water (30 mL) and extracted with CH₂Cl₂ (20 mL × 3). The combined organic phase was dried over MgSO₄ and solvent was removed under reduced pressure. The product was isolated by column chromatography (silica gel/hexane) in 77% yield.

Synthesis of (*E*)-2-fluoro-1-iodoalk-1-ene (3) with method C

Typical experimental procedure: Methyl undec-10-ynoate (293 mg, 2 mmol) and CH₂Cl₂ (6 mL) were introduced into a reaction vessel made of Teflon™ PFA and *p*-iodotoluene difluoride (3 mmol) in Et₃N–5HF (22 mL) was added at 0 °C. After stirring for 8 h at 0 °C, the reaction mixture was poured into water (30 mL) and extracted with CH₂Cl₂ (20 mL × 3). The combined organic phase was dried over MgSO₄ and concentrated under reduced pressure. The residue was dissolved in CH₂Cl₂ (5 mL) and added to a mixture of CuI (3.8 g, 20 mmol) and KI (3.32 g, 20 mmol) in CH₂Cl₂ (25 mL). The reaction mixture was stirred at room temperature for 72 h, poured into water (30 mL), and extracted with CH₂Cl₂ (20 mL × 3). The combined organic phase was dried over MgSO₄ and solvent was removed under reduced pressure. The product was isolated by column chromatography

(silica gel/hexane-Et₂O) in 80% yield.

(*E*)-2-Fluorododec-1-enyl(4-methylphenyl)iodonium fluoride (3a).

$\delta_{\text{H}}(\text{CDCl}_3)$ 0.87 (3H, t, J 7.1 Hz), 1.18–1.45 (16H, m), 2.37 (3H, s), 2.74 (2H, dt, $^3J_{\text{H-F}}$ 22.2, J 7.6 Hz, 3-H), 6.68 [1H, d, $^3J_{\text{H-F(olefin)}}$ 17.7 Hz, 1-H], 7.23 (2H, d, J 8.3 Hz), 7.85 (2H, d, J 8.3 Hz); $\delta_{\text{F}}(\text{CDCl}_3)$ -69.31 [1F, dt, $^3J_{\text{H-F}}$ 22.2, $^3J_{\text{H-F(olefin)}}$ 17.7 Hz].

(*E*)-2-Fluoro-1-iodododec-1-ene (1a).

$\delta_{\text{H}}(\text{CDCl}_3)$ 0.85 (3H, t, J 6.5 Hz, 12-H), 1.20–1.32 (14H, m), 1.44–1.56 (2H, m, 4-H), 2.46 (2H, dt, $^3J_{\text{H-F}}$ 23.0, J 7.6 Hz, 3-H), 5.63 [1H, d, $^3J_{\text{H-F(olefin)}}$ 17.7 Hz, 1-H]; $\delta_{\text{F}}(\text{CDCl}_3)$ -82.25 [1F, dt, $^3J_{\text{H-F}}$ 23.0, $^3J_{\text{H-F(olefin)}}$ 17.7 Hz]; $\delta_{\text{C}}(\text{CDCl}_3)$ 14.11, 22.69, 25.72, 28.75, 29.27, 29.31, 29.47, 29.56, 30.94 (d, $^2J_{\text{C-F}}$ 25.6 Hz, 3-C), 31.88, 54.65 (d, $^2J_{\text{C-F}}$ 39.7 Hz, 1-C), 164.22 (d, $^1J_{\text{C-F}}$ 264.4 Hz, 2-C); $\nu(\text{neat})/\text{cm}^{-1}$ 3080, 2920, 2845, 1645, 1465, 1430, 1380, 1125, 1085, 875, 770, 720; m/z 312 (M⁺, 18%), 185 (11), 165 (6), 123 (8), 109 (35), 95 (51), 83 (42), 69 (52), 55 (53), 43 (100) [Calc. for C₁₂H₂₂FI (*M*): 312.0750. Found: M⁺, 312.0742].

(*E*)-10-Fluoro-11-iodoundec-10-en-1-ol (1b).

Mp 30 °C; $\delta_{\text{H}}(\text{CDCl}_3)$ 1.27–1.40 (11H, m), 1.51–1.61 (4H, m), 2.50 (2H, dt, $^3J_{\text{H-F}}$ 22.4, J 7.6 Hz, 9-H), 3.64 (2H, t, J 6.6 Hz, 1-H), 5.67 [1H, d, $^3J_{\text{H-F(olefin)}}$ 17.8 Hz, 11-H]; $\delta_{\text{F}}(\text{CDCl}_3)$ -82.50 [1F, dt, $^3J_{\text{H-F}}$ 22.4, $^3J_{\text{H-F(olefin)}}$ 17.8 Hz]; $\delta_{\text{C}}(\text{CDCl}_3)$ 25.66 (2C), 28.65, 29.14, 29.31, 29.36, 30.88 (d, $^2J_{\text{C-F}}$ 26.4 Hz, 9-C), 32.74, 54.67 (d, $^2J_{\text{C-F}}$ 39.7 Hz, 11-C), 63.03, 164.63 (d, $^1J_{\text{C-F}}$ 264.4 Hz, 10-C); $\nu(\text{neat})/\text{cm}^{-1}$ 3330 (br), 3074, 2927, 2854, 1649, 1463, 1429, 1119, 1077, 1051, 870, 771, 714; m/z 314 (M⁺, 0.1%), 277 (3), 235 (1), 221 (2), 212 (1), 198 (64), 185 (18), 167 (12), 159 (3), 149 (76), 121 (14), 107 (36), 99 (46), 81 (66), 69 (75), 55 (100), 41 (82) [Calc. for C₁₁H₂₀FIO (*M*): 314.0543. Found: M⁺, 314.0534].

(*E*)-11-Chloro-2-fluoro-1-iodoundec-1-ene (1c).

$\delta_{\text{H}}(\text{CDCl}_3)$ 1.30–1.44 (10H, m), 1.52–1.59 (2H, m, 4-H), 1.73–1.81 (2H, m, 10-H), 2.50 (2H, dt, $^3J_{\text{H-F}}$ 22.4, J 7.3 Hz, 3-H), 3.53 (2H, t, J 6.6 Hz, 11-H), 5.67 [1H, d, $^3J_{\text{H-F(olefin)}}$ 17.8 Hz, 1-H]; $\delta_{\text{F}}(\text{CDCl}_3)$ -82.35 [1F, dt, $^3J_{\text{H-F}}$ 22.4, $^3J_{\text{H-F(olefin)}}$ 17.8 Hz]; $\delta_{\text{C}}(\text{CDCl}_3)$ 25.66, 26.83, 28.64, 28.80, 29.12, 29.25, 30.90 (d, $^2J_{\text{C-F}}$ 26.4 Hz, 3-C), 32.60, 45.15, 54.73 (d, $^2J_{\text{C-F}}$ 40.5 Hz, 1-C), 164.13 (d, $^1J_{\text{C-F}}$ 264.4 Hz, 2-C); $\nu(\text{neat})/\text{cm}^{-1}$ 3074, 2929, 2855, 1649, 1463, 1430, 1309, 1131, 1107, 1073, 875, 772, 726; m/z 332 (M^+ , 33%), 273 (3), 198 (4), 185 (20), 169 (4), 143 (13), 128 (9), 109 (35), 95 (40), 81 (90), 69 (81), 55 (100), 41 (75) [Calc. for $\text{C}_{11}\text{H}_{19}\text{ClFI}$ (M): 332.0204. Found: M^+ , 332.0204].

(*E*)-3-Cyclohexyl-2-fluoro-1-iodoprop-1-ene (1d).

$\delta_{\text{H}}(\text{CDCl}_3)$ 0.97-1.31 (5H, m), 1.60-1.78 (6H, m), 2.41 (2H, dd, J 7.1, $^3J_{\text{H-F}}$ 23.7 Hz, 3-H), 5.72 [1H, d, $^3J_{\text{H-F(olefin)}}$ 18.0 Hz, 1-H]; $\delta_{\text{F}}(84.67 \text{ MHz, CDCl}_3)$ -79.50 [1F, dt, $^3J_{\text{H-F}}$ 23.7, $^3J_{\text{H-F(olefin)}}$ 18.0 Hz]; $\nu(\text{neat})/\text{cm}^{-1}$ 3085, 2930, 2855, 1652, 1455, 1438, 1140, 1086, 875, 765; [Calc. for $\text{C}_9\text{H}_{14}\text{FI}$ (M): 286.0124. Found: M^+ , 268.0121].

2-[(*E*)-9-Fluoro-10-iododec-9-enyl]-4,4,5,5-tetramethyl-[1,3]dioxolane (1e).

$\delta_{\text{H}}(\text{CDCl}_3)$ 1.19 (12H, s), 1.21-1.44 (10H, m), 1.50-1.62 (4H, m), 2.49 (2H, dt, J 7.6, $^3J_{\text{H-F}}$ 22.5 Hz), 5.03 (1H, t, J 5.1 Hz), 5.66 [1H, d, $^3J_{\text{H-F(olefin)}}$ 17.5 Hz]; $\delta_{\text{F}}(84.67 \text{ MHz, CDCl}_3)$ -82.34 [1F, dt, $^3J_{\text{H-F}}$ 22.5, $^3J_{\text{H-F(olefin)}}$ 17.5 Hz]; $\nu(\text{neat})/\text{cm}^{-1}$ 3087, 2976, 2928, 2856, 1738, 1649, 1463, 1405, 1366, 1161, 1132, 1078, 967, 772; [Calc. for $\text{C}_{17}\text{H}_{30}\text{FIO}_2$ (M): 412.1275. Found: M^+ , 412.1252].

Methyl (*E*)-10-fluoro-11-iodoundec-10-enoate (1f).

$\delta_{\text{H}}(\text{CDCl}_3)$ 1.28–1.39 (8H, br s), 1.51–1.64 (4H, m), 2.31 (2H, t, J 7.3 Hz, 2-H), 2.50 (2H, dt, $^3J_{\text{H-F}}$ 22.5, J 7.3 Hz, 9-H), 3.67 (3H, s, OMe), 5.67 [1H, d, $^3J_{\text{H-F(olefin)}}$ 17.8 Hz, 11-H]; $\delta_{\text{F}}(\text{CDCl}_3)$ -82.36 [1F, dt, $^3J_{\text{H-F}}$ 22.5, $^3J_{\text{H-F(olefin)}}$ 17.8 Hz]; $\delta_{\text{C}}(\text{CDCl}_3)$ 24.92, 25.68, 28.63, 29.07 (3C), 30.91 (d, $^2J_{\text{C-F}}$ 26.4 Hz,

9-C), 34.09, 51.46, 54.75 (d, $^2J_{C-F}$ 40.5 Hz, 11-C), 164.14 (d, $^1J_{C-F}$ 264.4 Hz, 10-C), 174.28; $\nu(\text{neat})/\text{cm}^{-1}$ 3080, 2930, 2855, 1735, 1645, 1460, 1440, 1365, 1255, 1205, 1175, 1140, 1105, 1075, 880, 775, 720; m/z 311 ($M^+ - \text{OMe}$, 20%), 215 (14), 195 (28), 180 (20), 163 (78), 155 (7), 145 (27), 135 (33), 121 (100), 111 (9), 95 (28), 87 (37), 81 (56), 74 (77), 67 (27), 55 (78), 41 (52) [Calc. for $C_{11}H_{17}FIO$ ($M^+ - \text{OMe}$): 311.0308. Found: $M^+ - \text{OMe}$, 311.0321].

(*E*)-12-Fluoro-13-iodo-2,2-dimethyltridec-12-en-3-one (1g).

$\delta_H(\text{CDCl}_3)$ 1.13 (9H, s, ^tBu), 1.23–1.39 (8H, m), 1.51–1.58 (4H, m), 2.45–2.54 (4H, m), 5.66 [1H, d, $^3J_{H-F(\text{olefin})}$ 17.8 Hz, 13-H]; $\delta_F(\text{CDCl}_3)$ 82.48 [1F, dt, $^3J_{H-F}$ 23.3, $^3J_{H-F(\text{olefin})}$ 17.7 Hz]; $\delta_C(\text{CDCl}_3)$ 23.88, 25.68, 26.41 (3C), 28.66, 29.12, 29.25, 29.33, 30.90 (d, $^2J_{C-F}$ 26.5 Hz, 11-C), 36.40, 44.08, 54.72 (d, $^2J_{C-F}$ 40.5 Hz, 13-C), 164.15 (d, $^1J_{C-F}$ 264.4 Hz, 12-C), 216.10; $\nu(\text{neat})/\text{cm}^{-1}$ 3069, 2963, 2930, 2856, 1707, 1649, 1478, 1462, 1365, 1112, 1066, 771; m/z 368 (M^+ , 0.2%), 311 (41), 241 (17), 185 (6), 135 (11), 121 (10), 99 (16), 93 (10), 85 (18), 67 (11), 57 (100), 41 (34) [Calc. for $C_{15}H_{26}FIO$ (M): 368.1012. Found: M^+ , 368.1014].

(*E*)-1-Fluoro-1-phenenyl-2-iodoethene (1h).

$\delta_H(\text{CDCl}_3)$ 6.14 [1H, d, $^3J_{H-F(\text{olefin})}$ 19.5 Hz, 2-H], 7.42–7.81 (5H, m, Ph); $\delta_F(\text{CDCl}_3)$ -76.58 [1F, dt, $^3J_{H-F(\text{olefin})}$ 19.5 Hz]; $\delta_C(\text{CDCl}_3)$ 53.78 (d, $^2J_{C-F}$ 44.6 Hz, 2-C), 128.14 (2C), 128.58 (2C, d, $^3J_{C-F}$ 5.0 Hz, ortho), 130.20, 131.22 (d, $^2J_{C-F}$ 29.2 Hz, ipso), 158.86 (d, $^1J_{C-F}$ 256.0 Hz, 1-C); $\nu(\text{neat})/\text{cm}^{-1}$ 3066, 1637, 1599, 1492, 1445, 1303, 1280, 1146, 1047, 1025, 920, 799, 768, 691; m/z 248 (M^+ , 100%), 229 (24), 121 (50), 102 (54), 75 (19), 51 (13) [Calc. for C_8H_6FI (M): 247.9498. Found: M^+ , 247.9523].

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16. The stereochemistry and selectivity of **3a** was determined as follows; the obtained crude reaction mixture of **3a** was poured into water and extracted with dichloromethane. The organic phase was dried over MgSO₄ and concentrated under reduced pressure. From the ¹H NMR of the residue, a vinylic hydrogen signal was observed at 6.73 ppm with a 15.1 Hz coupling constant. Since the coupling constant was in good agreement with the reported data of (*E*)-2-fluoro-1-iodohept-1-ene,⁹ the stereochemistry of the double bond was determined as (*E*)-configuration. The stereoselectivity was determined from the ¹H NMR and ¹⁹F NMR.
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Chapter 2

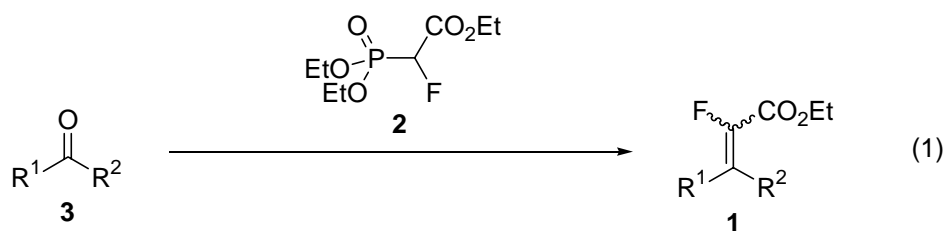
Stereoselective Synthesis of (*E*)- β -Fluoro- α,β -unsaturated Esters by Pd-Catalyzed Methoxycarbonylation of (*E*)-2-Fluoroalk-1-enyliodonium Salts

Abstract

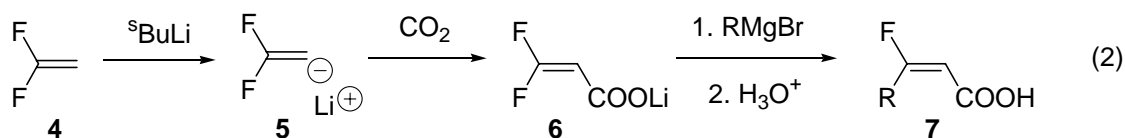
The Pd-catalyzed methoxycarbonylation of (*E*)-2-fluoro-1-iodoalk-1-enyliodonium salts with CO and methanol proceeded at room temperature to give (*E*)- β -fluoro- α,β -unsaturated esters stereoselectively (*E* / *Z* \geq 98 / 2).

Introduction

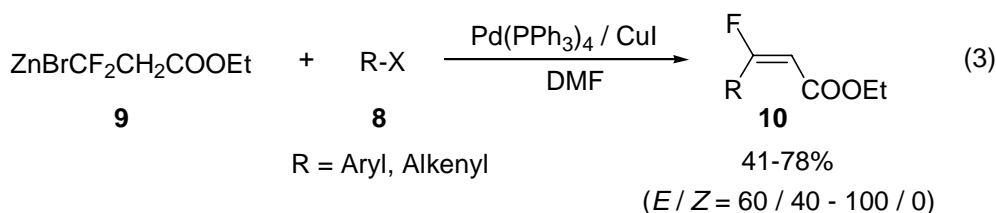
α -Fluoro- α,β -unsaturated esters (**1**) have been used as building blocks or key intermediates for the synthesis of fluorinated analogs of natural compounds¹ because they can be readily obtained by the Horner-Wadsworth-Emmons reaction using ethyl 2-fluorodiethylphosphonoacetate (**2**) with carbonyl compounds (**3**) [Eq (1)].²



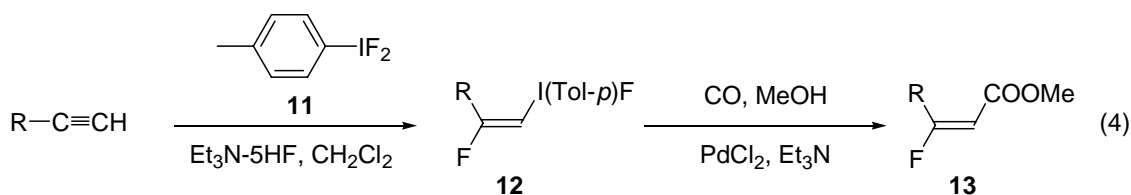
On the contrary, β -fluoro- α,β -unsaturated esters have been scarcely used for organic synthesis because effective methods for their preparation were unknown. To our knowledge, only two examples were published on the synthesis of β -fluoro- α,β -unsaturated esters or carboxylic acids. Normant *et al.* reported that β -fluoro- α,β -unsaturated carboxylic acid (**7**) could be obtained in moderate yield from 1,1-difluoroethylene (**4**) [Eq. (2)].³ Initially, compound **4** was converted to 2,2-difluorovinyl lithium (**5**) by treatment with ^sBuLi, and **5** was carboxylated with CO₂ to give lithium 2,2-difluoroacrylate (**6**). The addition of a Grignard reagent to **6** gave **7** via elimination of a fluoride anion from **6**. Recently, Qing *et al.* reported that the cross-coupling reaction of aryl or alkenyl halides (**8**) with 2-ethoxycarbonyl-1,1-difluoroethane zinc bromide (ZnBrCF₂CH₂COOEt) (**9**) gave β -fluoro- α,β -unsaturated esters (**10**) in moderate yields [Eq. (3)].⁴ These two reactions favorably afforded (*E*)- β -fluoro- α,β -unsaturated esters or carboxylic acids; however, the stereoselectivity was not high.



R	Yield / %	E / Z
Et	60	87 / 13
Bu	70	82 / 18
Ph	51	87 / 13



On the other hand, it is well known that alkenyl halides⁵ or iodonium salts⁶ can be converted to the corresponding carboxylic esters by the reaction with CO in alcohol in the presence of a Pd catalyst. Recently, the author found that *p*-iodotoluene difluoride (**11**) adds to terminal alkynes to give (*E*)- β -fluoroalkenyliodonium salts (**12**) stereoselectively (*E*/*Z* \geq 98 / 2) as shown in Chapter 1. In this chapter the stereoselective synthesis of (*E*)- β -fluoro- α,β -unsaturated esters (**13**) by the Pd-catalyzed carbonylation using **12** is described [Eq. (4)].



Results and Discussion

The methoxycarbonylation using alkenyliodonium salts with CO and methanol has been shown by Ochiai *et al.*^{6b} The reaction could be carried out at room temperature to give α,β -unsaturated esters in good yields. Initially, the methoxycarbonylation reaction of (*E*)- β -fluorododecenyliodonium salt (**12a**), prepared from dodec-1-yne, was examined under various reaction conditions (Table 1).⁶ Recently, the alkoxy carbonylation of 1,2-difluoro-1-iodoalk-1-enes was reported to proceed under the conditions of high temperature and high CO pressure.⁷ The methoxycarbonylation reaction using **12a** proceeded at room temperature and under 1 atm of CO to provide methyl (*E*)-3-fluorododec-2-enoate (**13a**) stereoselectively (*E* / *Z* \geq 98 / 2)⁶ with methyl 4-methylbenzoate (**14**) as a minor product.⁸ The application of higher temperature (Entries 6 and 9) or higher CO pressure (Entry 5) could not improve the yield of **13**. As for the catalyst, PdCl₂ was found to be more effective than Pd(OAc)₂, and 1 mol% of the Pd catalyst gave better results than 5 mol% of it (Entry 7). When the reaction was carried out at room temperature under 1 atm of CO using 1 mol% of PdCl₂ and 1 eq. of Et₃N, the best result was obtained (Entry 7).

Table 1. Synthesis of methyl (*E*)-3-fluorotridec-2-enoate (**13a**)^a

$C_{10}H_{21}-C\equiv CH \xrightarrow[Et_3N-5HF, CH_2Cl_2]{\mathbf{11}} \xrightarrow[Pd\ cat., R_3N]{CO, MeOH} \begin{matrix} C_{10}H_{21} & COOMe \\ & / \\ & C=C \\ & \backslash \\ F & \end{matrix} + p\text{-Tol-COOMe}$

13a **14**

Entry	Catalyst (mol%)	R ₃ N (eq.)	Temp.	Yield / % ^b
1	Pd(OAc) ₂ , (1)	Et ₃ N (1)	r.t.	54 (4)
2	Pd(OAc) ₂ , (5)	Et ₃ N (1)	r.t.	46 (4)
3	Pd(OAc) ₂ , (5)	Et ₃ N (3)	r.t.	28 (33)
4	Pd(OAc) ₂ , (5)	Bu ₃ N (1)	r.t.	44 (6)
5	Pd(OAc) ₂ , (5)	Et ₃ N (1)	r.t.	47 (trace) ^c
6	Pd(OAc) ₂ , (5)	Et ₃ N (1)	50 °C	44 (6)
7	PdCl ₂ , (1)	Et ₃ N (1)	r.t.	58 (3)
8	PdCl ₂ , (5)	Et ₃ N (1)	r.t.	50 (12)
9	PdCl ₂ , (5)	Et ₃ N (1)	50 °C	54 (13)

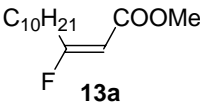
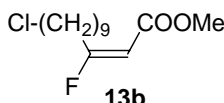
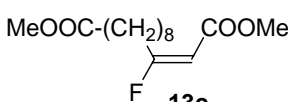
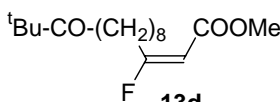
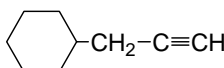
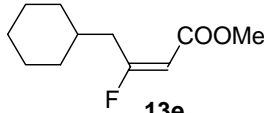
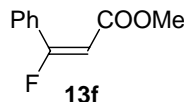
^a If otherwise not mentioned, the reaction was carried out under 1 atm of CO in 10 mL of MeOH for 12 h.

^b Isolated yield based on dodec-1-yne. In parenthesis, the yield of methyl 4-methylbenzoate.

^c The reaction was carried out under 10 atm of CO.

Under the same reaction conditions, a variety of alk-1-yne were converted to the corresponding (*E*)-β-fluoro-α,β-unsaturated esters (**13**) via fluoroalkenyliodonium salts (**12**) (Table 2). The yields are not high because the overall yields from the alk-1-yne were shown. The alkynes having functional groups such as a chlorine (Entry 2), ester (Entry 3) or ketone (Entry 4) can be converted to the corresponding fluorinated unsaturated esters (**13**) without protection of them. The isomeric purity of the products **13** was high (*E* / *Z* ≥ 98 / 2) and only a small amount of methyl 4-methylbenzoate (**14**) was formed (< 3%).

Table 2. Synthesis of (*E*)- β -fluoro- α,β -unsaturated esters

Entry	Alkyne	Product	Yield / % ^a
1	$C_{10}H_{21}-C\equiv CH$	 13a	58
2	$Cl-(CH_2)_9-C\equiv CH$	 13b	66
3	$MeOOC-(CH_2)_8-C\equiv CH$	 13c	60
4	$tBu-CO-(CH_2)_8-C\equiv CH$	 13d	51
5	 $CH_2-C\equiv CH$	 13e	57
6	$Ph-C\equiv CH$	 13f	57

^a Isolation yields based on alkyne used.

Reaction mechanism

A plausible reaction mechanism is shown in Figure 1.^{5,9} Initially, the highly electrophilic hypervalent iodine group¹⁰ of fluoroalkenyliodonium salt (**12**) added oxidatively to the Pd(0) to give an intermediate (**15**). In the next step, the Pd reacted with the alkenyl group according to “*path a*” to produce an alkenylpalladium intermediate (**16a**) along with generation of iodotoluene. Then, the insertion of carbon monoxide and addition of methanol occurred to give intermediate (**17a**). The following reductive elimination of the Pd catalyst produced (*E*)- β -fluoro- α,β -unsaturated ester (**13**). When the Pd of **5** reacted with the tolyl group instead of the alkenyl group according to “*path b*”, tolylpalladium intermediate (**16b**) should be given. The following insertion of carbon monoxide, addition of methanol and reductive elimination of the Pd catalyst produced 4-methyl benzoate (**14**). It was reported that the alkoxy carbonylation using alkenyl(phenyl)iodonium salts⁶ gave α,β -unsaturated esters and iodobenzene because the iodobenzene has higher leaving ability¹⁰ than the iodoalkene. For the same reason, the coupling reaction of **12** probably gave **13** through “*path a*”.

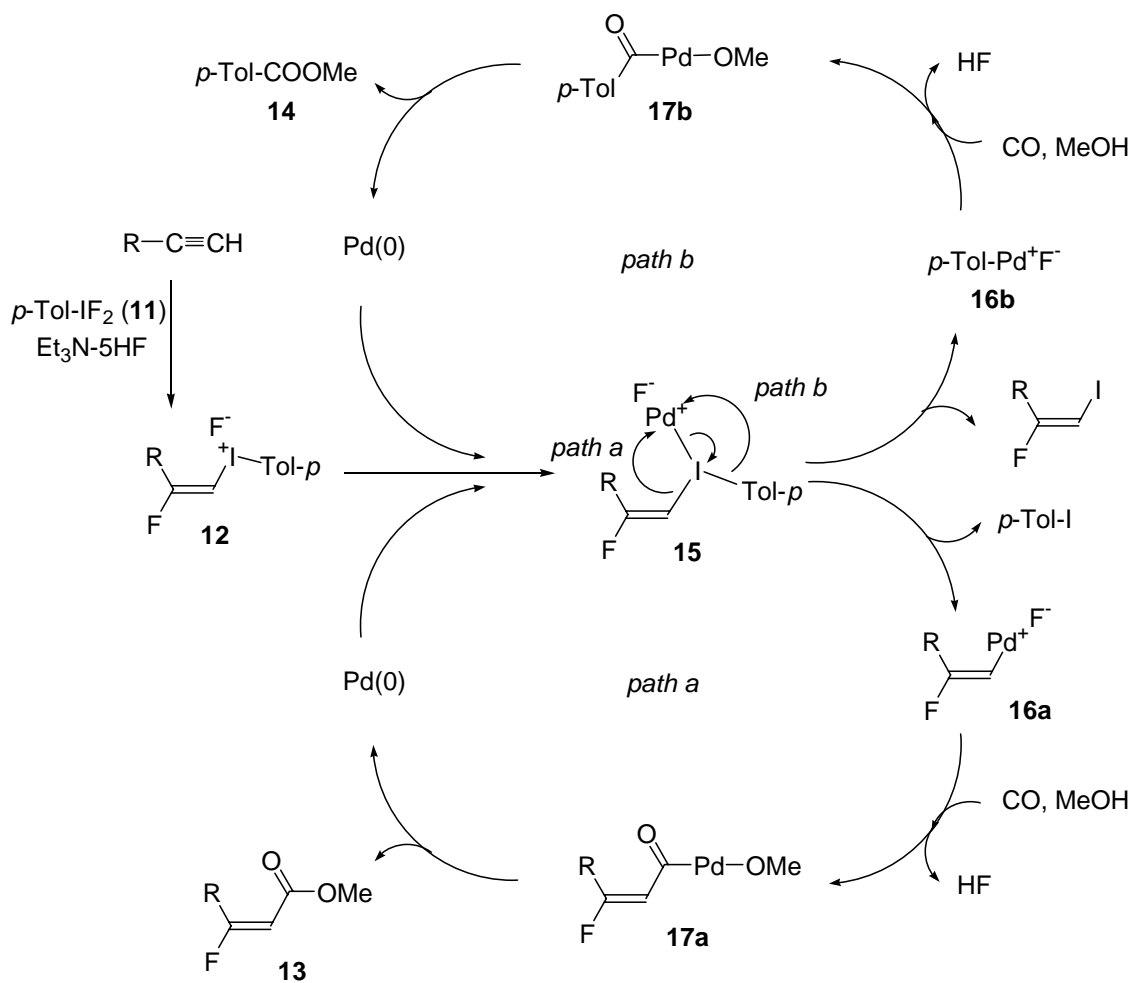


Figure 1.

Experimental

General

IR spectra were recorded using a JASCO FT/IR-410. ^1H NMR (400 MHz) and ^{19}F NMR (376 MHz) spectra were recorded in CDCl_3 on a JEOL JNM-A400II FT NMR and chemical shifts, δ , are referred to TMS (^1H) and CFCl_3 (^{19}F). EI low- and high-resolution mass spectra were measured on a JEOL JMS-700TZ, JMS-FABmate or JMS-HX110. For column chromatography, Merck silica gel 7734 was used, and Merck silica gel 5715 for analytical thin layer chromatography were used. PdCl_2 , $\text{Pd}(\text{OAc})_2$ and phenylacetylene were purchased from Tokyo Kasei Co., Ltd., and used without further purification. Preparation of $\text{Et}_3\text{N}\cdot 5\text{HF}$, dodec-1-yne, 3-cyclohexylprop-1-yne, 11-chloroundec-1-yne, methyl undec-10-ynoate and 2,2-dimethyltridec-12-yn-3-one were shown in Chapter 1.

Synthesis of (*E*)- β -fluoro- α,β -unsaturated esters (**13**)

A typical procedure is as follows. To a CH_2Cl_2 (3 mL) solution of dodec-1-yne (166 mg, 1 mmol) in a reaction vessel made of TeflonTM PFA, was added a $\text{Et}_3\text{N}\cdot 5\text{HF}$ solution (11 mL) of *p*-iodotoluene difluoride (1.5 mmol) at 0 °C. After stirring at 0 °C for 2 h, the reaction was quenched by the addition of water (10 mL). The mixture was extracted with CH_2Cl_2 (10 mL \times 3), dried over MgSO_4 , and concentrated under reduced pressure to give crude (*E*)-2-fluorododec-1-enyliodonium salt (**12a**), which was used for the next step without purification. In a glass vessel fitted with a balloon (3 L) and a septum inlet, PdCl_2 (2 mg, 0.01 mmol) was placed. After replacing the atmosphere of the vessel with CO, the balloon was filled with CO. The crude iodonium salt **12a** and Et_3N (101 mg, 1 mmol) in MeOH (10 mL) were then introduced into the reaction vessel through the septum. The reaction mixture was stirred at room temperature for 12 h and then poured into water (10 mL). The product was extracted with ether (10 mL \times 3) and the combined organic phases were dried over MgSO_4 . After

concentration under reduced pressure, purification of the product by column chromatography (silica gel/hexane-diethyl ether) gave methyl (*E*)-3-fluoro-2-tridecenoate (**13a**) in 58% yield with a trace amount of methyl 4-methylbenzoate as a by-product.

Methyl (*E*)-3-fluorotridec-2-enoate (13a).

¹H NMR (CDCl₃) δ_H 0.88 (3H, t, *J* 7.1 Hz), 1.19-1.44 (12H, m), 1.55-1.62 (4H, m), 2.80 (2H, dt, *J* 7.6, ³*J*_{H-F} 25.6 Hz), 3.71 (3H, s), 5.56 [1H, d, ³*J*_{H-F(olefin)} 19.5 Hz]; ¹⁹F NMR (84.67 MHz, CDCl₃/CCl₃F) δ_F -76.03 [1F, dt, ³*J*_{H-F} 25.6, ³*J*_{H-F(olefin)} 19.5 Hz]; ν(neat): 2926, 2855, 1729, 1674, 1437, 1367, 1133, 1097, 1033, 933, 852 cm⁻¹; HRMS (EI) calcd for C₁₄H₂₅O₂F 244.1839, Found 244.1841.

Methyl (*E*)-12-chloro-3-fluorododec-2-enoate (13b).

¹H NMR (CDCl₃) δ_H 1.30-1.78 (14H, m), 2.80 (2H, dt, *J* 7.6, ³*J*_{H-F} 25.6 Hz), 3.53 (2H, t, *J* 6.6 Hz), 3.71 (3H, s), 5.57 [1H, d, ³*J*_{H-F(olefin)} 19.5 Hz]; ¹⁹F NMR (84.67 MHz, CDCl₃/CCl₃F) δ_F -75.90 [1F, dt, ³*J*_{H-F} 25.6, ³*J*_{H-F(olefin)} 19.5 Hz]; ν(neat): 2932, 2857, 1726, 1673, 1437, 1367, 1280, 1137, 1115, 1032, 932, 852 cm⁻¹; HRMS (EI) calcd for C₁₃H₂₂O₂FCl 264.1292, Found 264.1317.

Methyl (*E*)-11-methoxycarbonyl-3-fluoroundec-2-enoate (13c).

¹H NMR (CDCl₃) δ_H 1.30-1.60 (8H, m), 1.56-1.63 (4H, m), 2.30 (2H, t, *J* 7.4 Hz), 2.80 (2H, dt, *J* 7.6, ³*J*_{H-F} 25.6 Hz), 3.67 (3H, s), 3.71 (3H, s), 5.56 [1H, d, ³*J*_{H-F(olefin)} 19.3 Hz]; ¹⁹F NMR (84.67 MHz, CDCl₃/CCl₃F) δ_F -75.85 [1F, dt, ³*J*_{H-F} 25.6, ³*J*_{H-F(olefin)} 19.3 Hz]; ν(neat): 2933, 2857, 1738, 1728, 1673, 1437, 1367, 1196, 1139, 1118, 1032, 932, 852 cm⁻¹; HRMS (EI) calcd for C₁₄H₂₃O₄F 274.1580, Found 274.1599.

Methyl (*E*)-3-fluoro-13,13-dimethyl-12-oxotetradec-2-enoate (13d).

¹H NMR (CDCl₃) δ_H 1.10 (9H, s), 1.23-1.34 (8H, m), 1.49-1.59 (4H, m), 2.44

(2H, t, J 7.3 Hz), 2.77 (2H, dt, J 7.3, $^3J_{\text{H-F}}$ 25.9 Hz), 3.68 (3H, s), 5.53 [1H, d, $^3J_{\text{H-F(olefin)}}$ 19.5 Hz]; ^{19}F NMR (84.67 MHz, $\text{CDCl}_3/\text{CCl}_3\text{F}$) δ_{F} -75.85 [1F, dt, $^3J_{\text{H-F}}$ 25.9, $^3J_{\text{H-F(olefin)}}$ 19.5 Hz]; $\nu(\text{neat})$: 2933, 2857, 1727, 1707, 1673, 1437, 1366, 1139, 1033, 852 cm^{-1} ; HRMS (EI) calcd for $\text{C}_{17}\text{H}_{29}\text{O}_3\text{F}$ 300.2101, Found 300.2099.

Methyl (*E*)-4-cyclohexyl-3-fluorobut-2-enoate (13e).

^1H NMR (CDCl_3) δ_{H} 1.05-1.24 (5H, m), 1.69-1.75 (6H, m), 2.71 (2H, dd, J 7.1, $^3J_{\text{H-F}}$ 27.0 Hz), 3.70 (3H, s), 5.60 [1H, d, $^3J_{\text{H-F(olefin)}}$ 19.8 Hz]; ^{19}F NMR (84.67 MHz, $\text{CDCl}_3/\text{CCl}_3\text{F}$) δ_{F} -72.87 [1F, dt, $^3J_{\text{H-F}}$ 27.0, $^3J_{\text{H-F(olefin)}}$ 19.8 Hz]; $\nu(\text{neat})$: 2926, 2853, 1727, 1670, 1441, 1280, 1139, 1098, 1035, 852 cm^{-1} ; HRMS (EI) calcd for $\text{C}_{11}\text{H}_{17}\text{O}_2\text{F}$ 200.1213, Found 200.1195.

Methyl (*E*)-3-fluoro-3-phenylprop-2-enoate (13f).

^1H NMR (CDCl_3) δ_{H} 3.69 (3H, s), 5.88 [1H, d, $^3J_{\text{H-F(olefin)}}$ 20.5 Hz], 7.38-7.72 (5H, m); ^{19}F NMR (84.67 MHz, $\text{CDCl}_3/\text{CCl}_3\text{F}$) δ_{F} -76.29 [1F, d, $^3J_{\text{H-F(olefin)}}$ 20.5 Hz]; $\nu(\text{neat})$: 3066, 2952, 2846, 1730, 1657, 1436, 1366, 1283, 1233, 1152, 1068, 931, 852 cm^{-1} ; HRMS (EI) calcd for $\text{C}_{10}\text{H}_9\text{O}_2\text{F}$ 180.0587, Found 180.0576.

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Chapter 3

Regio- and Stereoselective Synthesis of Fluoroalkadienes via Pd-Catalyzed Coupling Reaction of (*E*)-2-Fluoroalk-1-enyliodonium Salts with α,β -Unsaturated Carbonyl Compounds or Organostannanes

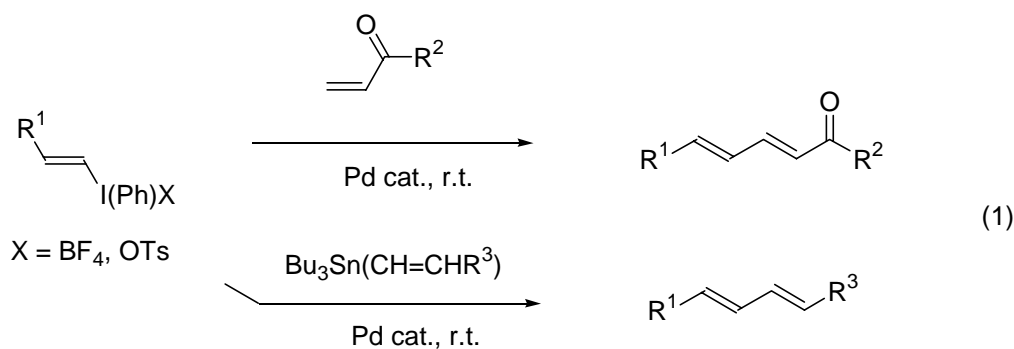
Abstract

(*E,E*)- δ -Fluoro- $\alpha,\beta,\gamma,\delta$ -unsaturated carbonyl compounds and (*E*)-4-fluoroalka-1,3-dienes were stereoselectively synthesized by the Pd-catalyzed coupling reaction of (*E*)-2-fluoroalk-1-enyl(4-methylphenyl)iodonium fluorides with α,β -unsaturated carbonyl compounds (Heck reaction) and tributylvinylstannane (Stille reaction), respectively. Both of the coupling reactions smoothly proceeded at room temperature. The potential versatility of the reaction was demonstrated by the synthesis of a fluorinated analogue of a natural product bearing a conjugated diene structure.

Introduction

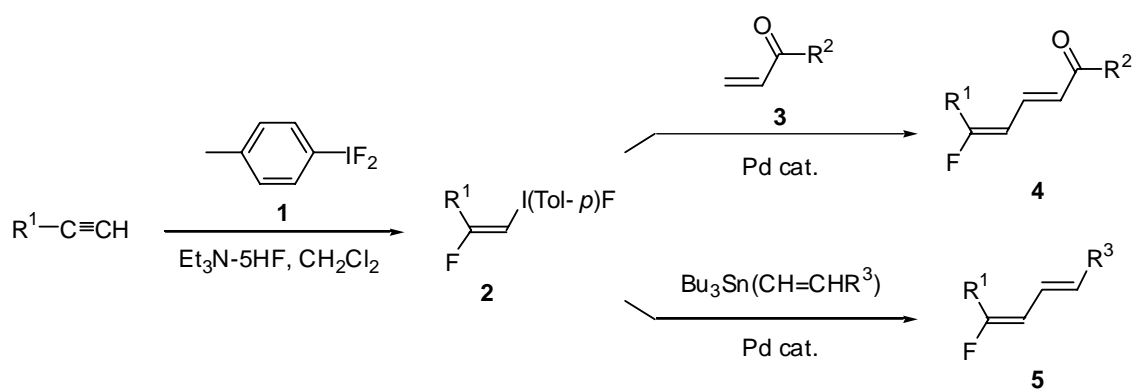
The introduction of a fluorine atom into the conjugated double bonds of bioactive compounds is known to be effective to increase the stability and to enhance the bioactivities of these compounds.¹ Therefore, much effort has been made towards the stereoselective synthesis of fluorinated polyenes, and some successful results have been reported.² Since the efficacy of a bioactive compound having a fluorinated polyene moiety is strongly affected by the position and stereochemistry of the fluorine atom,³ new methodologies for stereoselective fluoropolyene synthesis are required in order to introduce a fluorine atom into any position on the conjugated double bonds of natural compounds.

In Chapter 1, the author presented that (*E*)-2-fluoroalk-1-enyl(4-methylphenyl)iodonium fluorides (**2**) can be regio- and stereoselectively prepared by the reaction of alk-1-yne with *p*-iodotoluene difluoride (**1**) in the presence of Et₃N·5HF.⁴ On the other hand, Moriarty *et al.* reported the unusual high reactivity of hypervalent iodine compounds in the Pd-catalyzed Heck-type reaction⁵ and the Stille reaction.⁶ [Eq. (1)].



Therefore, the author applied the fluoroalkenyliodonium salts (**2**) to the Heck and the Stille reactions to develop new methodology applicable to the stereoselective synthesis of natural compound analogs having a fluorine atom on their conjugated double bonds (Scheme 1). The Heck

reaction of iodonium salts (**2**) with α,β -unsaturated carbonyl compounds (**3**) was carried out in the presence of $\text{Pd}(\text{OAc})_2$ and NaHCO_3 to give (*E,E*)- δ -fluoro- $\alpha,\beta,\gamma,\delta$ -unsaturated carbonyl compounds (**4**) stereoselectively in good yields. (*E,E*)-Fluoroalkadienes (**5**) were also stereoselectively obtained by the Stille reaction of **2** with alkenylstannanes. In this chapter, the details of these two reactions are described.



Scheme 1.

Results and Discussion

Heck-type reaction

(*E*)-2-Fluorodec-1-enyl(4-methylphenyl)iodonium fluoride (**2a**) was prepared by the reaction of dec-1-yne with *p*-iodotoluene difluoride (**1**) in the presence of Et₃N·5HF as shown in Chapter 1. The crude **2a** was used for the reaction with ethyl acrylate (**3a**) in the presence of a catalytic amount of Pd(OAc)₂ and 3 eq. of NaHCO₃ in DMF.⁵ The reaction was completed at room temperature in 2 h, and the desired ethyl (2*E*,4*E*)-4-fluorotrideca-2,4-dienoate (**4a**) was obtained in 55% yield based on the decyne. The stereochemistry of **4a** was determined as follows. The coupling constant between fluorine on C-5 and hydrogen on C-4 was 18.3 Hz which showed that the double bond at the γ,δ position had (*E*)-stereochemistry.⁷ This assignment was also supported by NOE experiment; an NOE was observed between a hydrogen on C-6 and a hydrogen on C-3 while no NOE was observed between a hydrogen on C-6 and a hydrogen on C-4 (Figure 1). The coupling constant between a hydrogen on C-2 and a hydrogen on C-3 was 14.9 Hz which showed that the newly formed double bond also had (*E*)-stereochemistry.

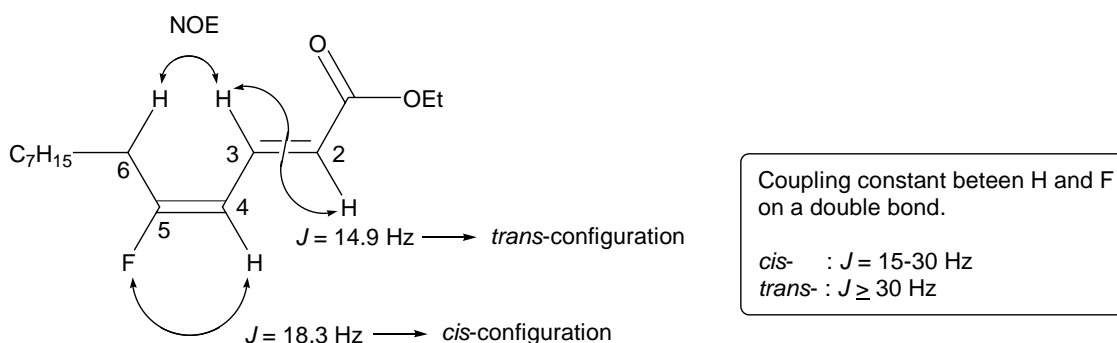
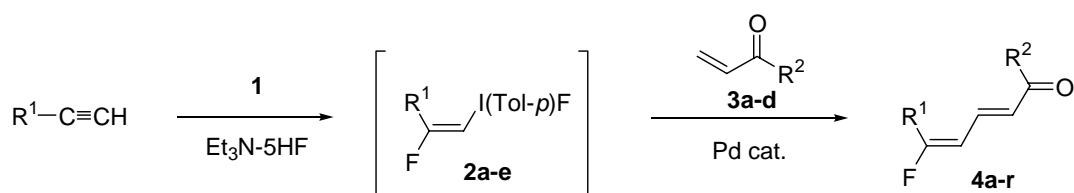


Figure 1.

The alkenyliodonium salts having functional groups such as an ester, ketone or chlorine prepared *in situ* from the corresponding alk-1-yne were subjected to the reaction with an ethyl acrylate (**3a**),

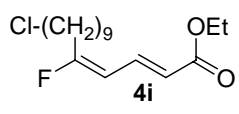
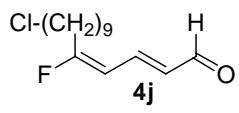
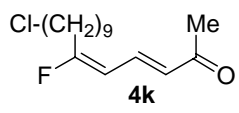
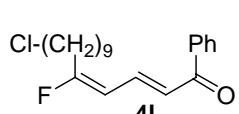
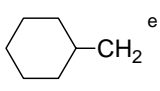
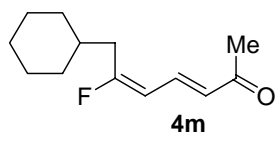
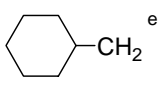
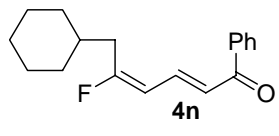
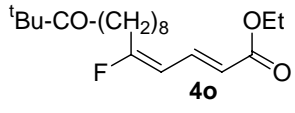
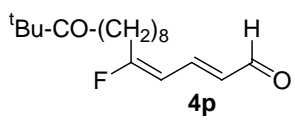
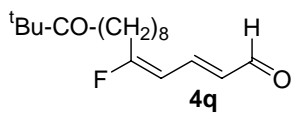
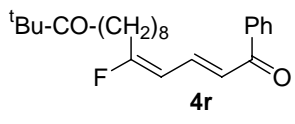
acrolein (**3b**), methyl vinyl ketone (**3c**) and phenyl vinyl ketone (**3d**) (Table 1). The expected δ -fluoro- $\alpha,\beta,\gamma,\delta$ -unsaturated carbonyl compounds (**4a-r**) could be obtained in 51-68% yields with high stereoselectivity (>98%). The yields are not high because they are the overall yields of two steps from alkynes.⁸ As for the by-products, β -tolyl- α,β -unsaturated carbonyl compounds, formed by the Heck-type reaction between **3** and the *p*-tolyl group on **2**, were obtained in 2-5% yield with a trace amount of the starting alkynes formed by the decomposition of **2**. Since the reaction proceeded under mild conditions, the functional groups in the substrates remained unchanged under the stated reaction conditions, and consequently, the polyfunctionalized fluoroalkadienes could be synthesized in a few steps with high selectivity. For the mechanism of the coupling reaction, refer to Chapter 2.

Table 1. Heck-type Coupling Reaction Using (*E*)-2-fluoroalkenyliodonium Salts^a

Entry	R ¹	R ²	Product	Yield / % ^b
1	C ₈ H ₁₇ ^c	OEt 3a		55
2	C ₈ H ₁₇ ^c	H 3b		54
3	C ₈ H ₁₇ ^c	Me 3c		53
4	C ₈ H ₁₇ ^c	Ph 3d		57
5	MeOOC-(CH ₂) ₈ ^d	OEt		56
6	MeOOC-(CH ₂) ₈ ^d	H		55
7	MeOOC-(CH ₂) ₈ ^d	Me		60
8	MeOOC-(CH ₂) ₈ ^d	Ph		68

a) The reaction conditions were described in following experimental section. b) Isolated yield based on alkyne used. c) To prepare **2a**, 2 h was taken. d) To prepare **2b** and **2c**, 8 h was taken.

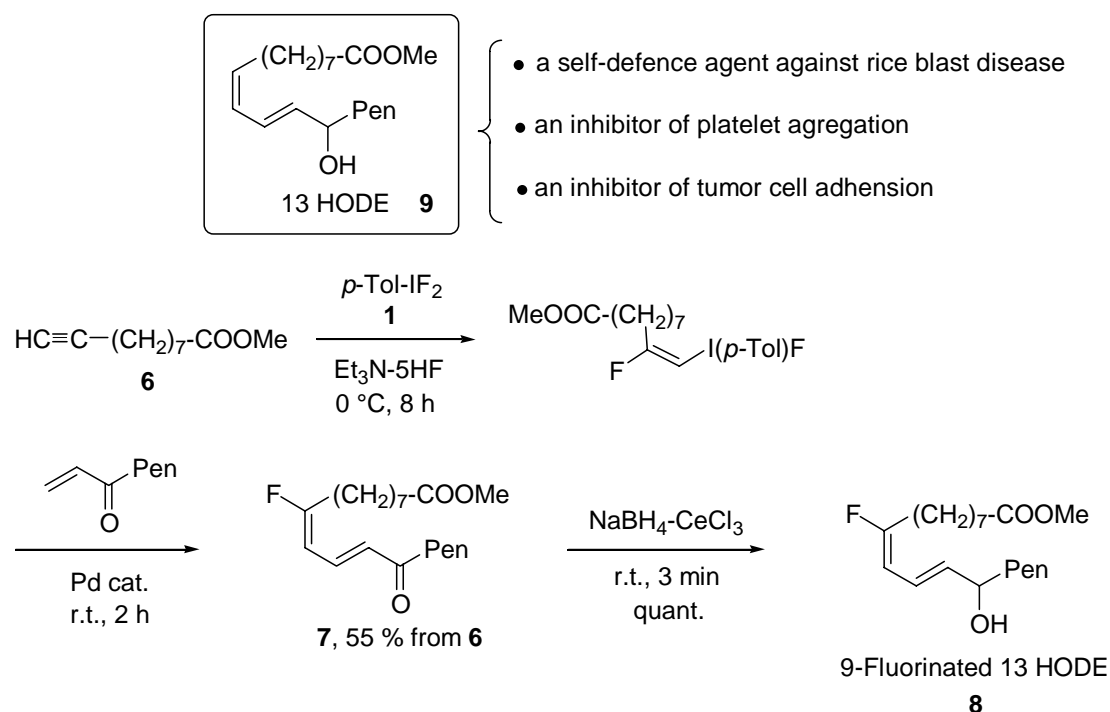
Table 1. (Continued)

Entry	R ¹	R ²	Product	Yield / % ^b
9	Cl-(CH ₂) ₉ ^d	OEt	 4i	61
10	Cl-(CH ₂) ₉ ^d	H	 4j	56
11	Cl-(CH ₂) ₉ ^d	Me	 4k	65
12	Cl-(CH ₂) ₉ ^d	Ph	 4l	54
13	 ^e	Me	 4m	51
14	 ^e	Ph	 4n	51
15	^t Bu-CO-(CH ₂) ₈ ^f	OEt	 4o	57
16	^t Bu-CO-(CH ₂) ₈ ^f	H	 4p	53
17	^t Bu-CO-(CH ₂) ₈ ^f	Me	 4q	61
18	^t Bu-CO-(CH ₂) ₈ ^f	Ph	 4r	66

e) To prepare **2d**, 12 h was taken. f) To prepare **2e**, 14 h was taken.

Application of the Heck-type coupling reaction using fluoroalkenyliodonium salt to the synthesis of a fluorinated analog of a natural compound

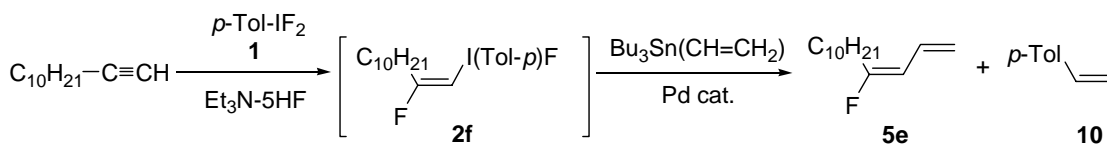
It is known that (9*Z*,11*E*)-13-hydroxyoctadeca-9,11-dienoic acid (13 HODE, **9**) has interesting bioactive properties;⁹ therefore, its fluorinated analogues are attractive targets for organic chemists.¹⁰ We attempted to synthesize the methyl ester of 9-fluoro-13 HODE (**8**) which has a fluorine atom on the conjugated double bond. Methyl dec-9-ynoate (**6**) was allowed to react with iodotoluene difluoride (**1**) in the presence of Et₃N·5HF and the resulting (*E*)-2-fluoroalk-1-enyliodonium fluoride was used for the Heck-type coupling reaction with oct-1-en-3-one in the presence of a Pd-catalyst to give the methyl (9*E*,11*E*)-9-fluoro-13-oxoocta-9,11-dienoate (**7**) in 55% yield from **6**. The desired methyl ester of 9-fluoro-13 HODE (**8**) was quantitatively obtained by reduction of the keto-function of **7** with NaBH₄ and CeCl₃ (Scheme 2).



Scheme 2.

Stille reaction

The cross-coupling reaction of (*E*)-2-fluorododec-1-enyl(4-methylphenyl)iodonium fluoride (**2f**) with tributylvinylstannane was carried out in the presence of PdCl₂(MeCN)₂, and the desired (*E*)-4-fluorotetradeca-1,3-diene (**5e**) was obtained in 51% yield from the dodecyne (Entry 1 in Table 2).⁶ According to the ¹H NMR spectrum of **5e**, it was confirmed that the reaction proceeded stereoselectively (*E* / *Z* ≥ 98 / 2). A by-product, *p*-vinyltoluene (4-methylstyrene) (**10**), formed by the reaction of tributylvinylstannane with the tolyl group on **2f**, was obtained in 10% yield. It was reported that no identifiable by-products formed in the reaction of the tributylvinylstannane with the unfluorinated (*E*)-alkenyl(phenyl)iodonium salts.⁶ The *cis*-substituted alkyl group to iodine¹¹ or a fluorine substituent in **2f** retarded the oxidative addition of the Pd catalyst to the iodine-alkenyl bond,^{2d-g,12} and the selective formation of **5e** was disturbed. Various kinds of Pd catalysts with or without CuI were used to improve the result, but the formation of **10** could not be suppressed. The best result was obtained when Bn(PPh₃)₂PdCl was used without CuI and **5e** was obtained in 61% yield based on dodec-1-yne with high stereoselectivity (>98%) along with the generation of 7% of **10**.

Table 2. Influence of Pd Catalyst in the Synthesis of Fluorodienes^a

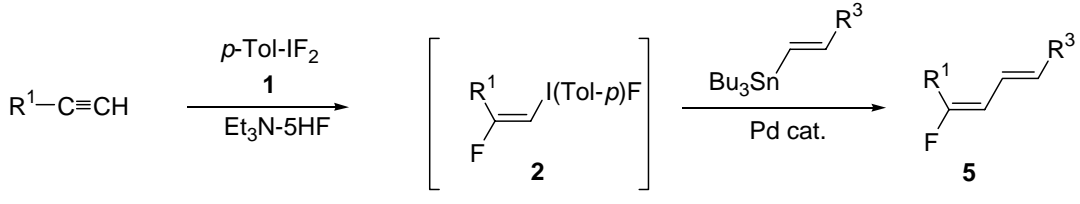
Entry	Pd cat.	CuI (mol%)	5e : 10 ^b	Yield of 5e / % ^c
1	(CH ₃ CN) ₂ PdCl ₂	—	80 : 20	51
2	Pd(PPh ₃) ₄	8	80 : 20	32
3	PdCl ₂	8	80 : 20	45
4	Bn(PPh ₃) ₂ PdCl	8	80 : 20	49
5	(CH ₃ CN) ₂ PdCl ₂	8	80 : 20	52
6	PdCl ₂	—	80 : 20	44
7	Bn(PPh ₃) ₂ PdCl	—	90 : 10	61

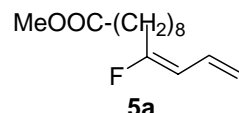
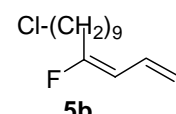
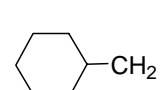
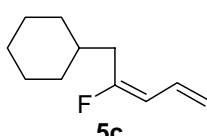
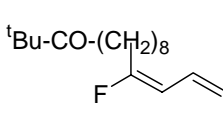
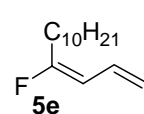
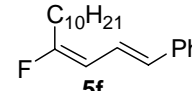
^a The reaction conditions were described in following experimental section. ^b Determined by GC analyses.

^c Isolated yield based on dodecyne used.

Various fluoroalkenyliodonium salts (**2**) were used for the cross-coupling reaction with organostannanes under the reaction conditions, and the corresponding fluoroalkadienes (**5a-e**) could be obtained in 59-65% yields with high stereoselectivity (Table 3). The reaction proceeded at room temperature and the various functional groups remained unchanged under the given reaction conditions (Entries 1, 2 and 4, Table 3). However, the application of **2** to the cross-coupling reaction with tributyl(β -styryl)stannane resulted in a poor yield of (1*E*,3*E*)-4-fluoro-1-phenyltetradec-1,3-diene (**5f**) (Entry 6). Since the reaction proceeded under mild conditions, protection of the functional groups in the substrates was not required. Thus, the polyfunctionalized fluoroalka-1,3-dienes were synthesized in good yields with high stereoselectivity.

Table 3. Synthesis of Fluorodienes (**5**)^a



Entry	R ₁	R ₃	Product	Yield / % ^b
1	MeOOC-(CH ₂) ₈	H	 5a	63(15)
2	Cl-(CH ₂) ₉	H	 5b	65(16)
3		H	 5c	62(13)
4	^t Bu-CO-(CH ₂) ₈	H	 5d	59(14)
5	C ₁₀ H ₂₁	H	 5e	61(7)
6	C ₁₀ H ₂₁	Ph	 5f	30(3)

^a The reaction conditions were described in following experimental section. ^b Isolated yield based on alkyne used. In parentheses, yield of tolylated products.

Conclusion

(*E,E*)- δ -Fluoro- $\alpha,\beta,\gamma,\delta$ -unsaturated carbonyl compounds (**4**) and (*E*)-4-fluoro-1,3-dienes (**5**) were stereoselectively obtained by the Heck-type reaction or the Stille reaction with the (*E*)-2-fluoroalk-1-enyliodonium fluorides (**2**) obtained from the alk-1-yne and *p*-iodotoluene difluoride (**1**). The reaction proceeded at room temperature and many functional groups in the substrate could tolerate the reaction conditions. Consequently, various kinds of fluoroalkadienes having functional groups could be synthesized, and the reaction was used for the synthesis of a fluorinated analog of a natural compound.

Experimental

General.

The IR spectra were recorded using a JASCO FT/IR-410. The ^1H NMR (400 MHz) and ^{19}F NMR (376 MHz) spectra were recorded in CDCl_3 on a JEOL JNM-A400II FT NMR and the chemical shifts, δ , are referred to TMS (^1H) and CFCl_3 (^{19}F), respectively. The EI-low and high-resolution mass spectra were measured on a JEOL JMS-700TZ, JMS-FABmate or JMS-HX110. The elemental microanalyses were done using a Yanagimoto CHN Corder MT-5. For column chromatography, Merck silica gel 7734 was used and for analytical thin layer chromatography, Merck silica gel 5715 was used. Methyl dec-9-ynoic acid was obtained by esterification of dec-9-ynoic acid prepared from dec-9-enoic acid as shown in Chapter 1. Dec-1-yne, dec-9-enoic acid, PdCl_2 , $(\text{CH}_3\text{CN})_2\text{PdCl}_2$, $\text{Pd}(\text{PPh}_3)_4$ and $\text{Pd}(\text{OAc})_2$ were purchased from Tokyo Kasei Co., Ltd., and used without further purification. Tributylvinylstannane¹³ and tributyl[(*E*)- β -styryl]stannane¹⁴ were prepared according to the literatures. Preparation of $\text{Et}_3\text{N}\cdot 5\text{HF}$, dodec-1-yne, 3-cyclohexylprop-1-yne, 11-chloroundec-1-yne, methyl undec-10-ynoate, 2,2-dimethyltridec-12-yn-3-one and *p*-iodotoluene difluoride (**1**) were shown in Chapter 1.

General procedure for (*E,E*)- δ -fluoro- $\alpha,\beta,\gamma,\delta$ -unsaturated carbonyl compounds (**4**)

To a CH_2Cl_2 solution (6 mL) of alk-1-yne (2 mmol) was added at 0 °C, a $\text{Et}_3\text{N}\cdot 5\text{HF}$ solution (22 mL) of *p*-iodotoluene difluoride prepared from *p*-iodotoluene (654 mg, 3 mmol). After stirring at 0 °C for 2-14 h, the reaction mixture was poured into water (40 mL) and the separated aqueous phase was extracted with CH_2Cl_2 (20 mL \times 3). The combined organic phase was dried over MgSO_4 and concentrated under reduced pressure. The remaining viscous yellow oil was washed with hexane (10 mL) and the hexane layer was removed by decantation. The residue was dissolved in

DMF (10 mL) and NaHCO₃ (504 mg, 6 mmol), Pd(OAc)₂ (31 mg, 0.14 mmol) and an α,β -unsaturated carbonyl compound (5 mmol) were added. The reaction mixture was stirred at room temperature for 2 h and saturated aqueous NH₄Cl (20 mL) was added. After extraction with ether (10 mL \times 3), the organic phase was dried over MgSO₄ and concentrated under reduced pressure. The product **4** was isolated by column chromatography (silica gel/hexane-ether). When acrolein was used as the carbonyl compound, 6 equivalents of NaHCO₃ to the alk-1-yne was necessary.

Ethyl (2*E*,4*E*)-5-fluorotrideca-2,4-dienoate (4a)

R_f 0.60 (hexane-ether 10:1); $\delta_{\text{H}}(\text{CDCl}_3)$ 0.88 (3H, t, J 7.1 Hz), 1.28-1.33 (13H, m), 1.53-1.61 (2H, m), 2.48 (2H, dt, J 7.6, $^3J_{\text{H-F}}$ 20.4 Hz), 4.21 (2H, q, J 7.1 Hz), 5.84 (1H, d, J 14.9 Hz), 5.86 [1H, dd, J 11.9, $^3J_{\text{H-F(olefin)}}$ 18.3 Hz], 7.31 (1H, dd, J 11.9, 14.9 Hz); $\delta_{\text{F}}(\text{CDCl}_3)$ -87.95 [1F, dt, $^3J_{\text{H-F(olefin)}}$ 18.3, $^3J_{\text{H-F}}$ 20.4 Hz]; $\delta_{\text{C}}(\text{CDCl}_3)$ 14.09, 14.32, 22.63, 26.33, 28.83 (d, $^2J_{\text{C-F}}$ 25.9 Hz), 28.94, 29.12, 29.24, 31.80, 60.31, 107.06 (d, $^2J_{\text{C-F}}$ 28.9 Hz), 120.10 (d, $^4J_{\text{C-F}}$ 9.9 Hz), 138.48 (d, $^3J_{\text{C-F}}$ 14.1 Hz), 166.94, 169.50 (d, $^1J_{\text{C-F}}$ 266.0 Hz); $\nu(\text{neat})/\text{cm}^{-1}$ 1718; [Calc. for C₁₅H₂₅FO₂ (*M*): 256.1832. Found: M⁺, 256.1853]; (Calc. for C₁₅H₂₅FO₂: C, 70.28; H, 9.83; F, 7.41. Found: C, 70.37; H, 9.79; F, 7.71%).

(2*E*,4*E*)-5-Fluorotrideca-2,4-dienal (4b)

R_f 0.38 (hexane-ether 5:1); $\delta_{\text{H}}(\text{CDCl}_3)$ 0.88 (3H, t, J 7.4 Hz), 1.32-1.34 (10H, m), 1.58-1.65 (2H, m), 2.50 (2H, dt, J 7.3, $^3J_{\text{H-F}}$ 23.4 Hz), 6.01 [1H, dd, J 11.9, $^3J_{\text{H-F(olefin)}}$ 18.0 Hz], 6.14 (1H, dd, J 7.8, 15.1 Hz), 7.16 (1H, dd, J 11.9, 15.1 Hz), 9.55 (1H, d, J 7.8 Hz); $\delta_{\text{F}}(\text{CDCl}_3)$ -82.58 [1F, dt, $^3J_{\text{H-F}}$ 18.0, $^3J_{\text{H-F(olefin)}}$ 23.4 Hz]; $\delta_{\text{C}}(\text{CDCl}_3)$ 14.02, 22.57, 26.21, 28.90, 28.93 (d, $^2J_{\text{C-F}}$ 24.7 Hz), 29.05, 29.15, 31.73, 107.68 (d, $^2J_{\text{C-F}}$ 29.7 Hz), 130.96 (d, $^4J_{\text{C-F}}$ 9.9 Hz), 145.99 (d, $^3J_{\text{C-F}}$ 14.0 Hz), 170.63 (d, $^1J_{\text{C-F}}$ 270.9 Hz), 192.85; $\nu(\text{neat})/\text{cm}^{-1}$ 1689; [Calc. for C₁₃H₂₁FO (*M*): 212.1576. Found: M⁺, 212.1585].

(3*E*,5*E*)-6-Fluorotetradeca-3,5-dien-2-one (4c)

R_f 0.36 (hexane-ether 5:1); $\delta_H(\text{CDCl}_3)$ 0.88 (3H, t, J 7.1 Hz), 1.27-1.30 (10H, m), 1.55-1.60 (2H, m), 2.26 (3H, s), 2.47 (2H, dt, J 7.6, $^3J_{\text{H-F}}$ 23.7 Hz), 5.87 [1H, dd, J 11.7, $^3J_{\text{H-F(olefin)}}$ 18.5 Hz], 6.16 (1H, d, J 15.3 Hz), 7.19 (1H, dd, J 11.7, 15.3 Hz); $\delta_F(\text{CDCl}_3)$ -85.62 [1F, dt, $^3J_{\text{H-F(olefin)}}$ 18.5, $^3J_{\text{H-F}}$ 23.7 Hz]; $\delta_C(\text{CDCl}_3)$ 14.06, 22.61, 26.28, 28.09, 28.89 (d, $^2J_{\text{C-F}}$ 25.6 Hz), 28.91, 29.09, 29.21, 31.78, 107.43 (d, $^2J_{\text{C-F}}$ 28.9 Hz), 128.93 (d, $^4J_{\text{C-F}}$ 10.7 Hz), 136.93 (d, $^3J_{\text{C-F}}$ 13.2 Hz), 170.18 (d, $^1J_{\text{C-F}}$ 267.6 Hz), 197.59; $\nu(\text{neat})/\text{cm}^{-1}$ 1653; [Calc. for $\text{C}_{14}\text{H}_{23}\text{FO}$ (M): 226.1733. Found: M^+ , 226.1736].

(2*E*,4*E*)-5-Fluoro-1-phenyltrideca-2,4-dien-1-one (4d)

R_f 0.56 (hexane-ether 5:1); $\delta_H(\text{CDCl}_3)$ 0.88 (3H, t, J 7.1 Hz), 1.27-1.31 (10H, m), 1.56-1.63 (2H, m), 2.52 (2H, dt, J 7.6, $^3J_{\text{H-F}}$ 23.7 Hz), 6.02 [1H, dd, J 12.2, $^3J_{\text{H-F(olefin)}}$ 18.3 Hz], 6.99 (1H, d, J 14.9 Hz), 7.46-7.58 (4H, m), 7.96 (2H, d, J 7.1 Hz); $\delta_F(\text{CDCl}_3)$ -85.22 [1F, dt, $^3J_{\text{H-F(olefin)}}$ 18.3, $^3J_{\text{H-F}}$ 23.7 Hz]; $\delta_C(\text{CDCl}_3)$ 14.06, 22.61, 26.40, 28.96, 29.00 (d, $^2J_{\text{C-F}}$ 24.3 Hz), 29.10, 29.23, 31.77, 107.91 (d, $^2J_{\text{C-F}}$ 28.9 Hz), 124.01 (d, $^4J_{\text{C-F}}$ 10.7 Hz), 128.31 (2C), 128.57 (2C), 132.71, 138.05, 138.73 (d, $^3J_{\text{C-F}}$ 13.3 Hz), 171.01 (d, $^1J_{\text{C-F}}$ 268.5 Hz), 189.75; $\nu(\text{neat})/\text{cm}^{-1}$ 1675; [Calcd for $\text{C}_{19}\text{H}_{25}\text{FO}$ (M): 288.1883. Found: M^+ , 288.1916]; (Calc. for $\text{C}_{19}\text{H}_{25}\text{FO}$: C, 79.13; H, 8.74; F, 6.59. Found: C, 79.04; H, 8.90; F, 6.58%).

Ethyl (2*E*,4*E*)-5-fluoro-13-methoxycarbonyltrideca-2,4-dienoate (4e)

R_f 0.47 (hexane-ether 2:1); $\delta_H(\text{CDCl}_3)$ 1.27-1.31 (8H, m), 1.53-1.64 (4H, m), 2.30 (2H, t, J 7.6 Hz), 2.45 (2H, dt, J 7.6, $^3J_{\text{H-F}}$ 23.4 Hz), 3.67 (3H, s), 4.21 (2H, q, J 7.1 Hz), 5.85 (1H, d, J 14.9 Hz), 5.87 [1H, dd, J 12.2, $^3J_{\text{H-F(olefin)}}$ 18.5 Hz], 7.31 (1H, dd, J 12.2, 14.9 Hz); $\delta_F(\text{CDCl}_3)$ -88.03 [1F, dt, $^3J_{\text{H-F(olefin)}}$ 18.5, $^3J_{\text{H-F}}$ 23.4 Hz]; $\delta_C(\text{CDCl}_3)$ 14.29, 24.87, 26.26, 28.78 (d, $^2J_{\text{C-F}}$ 25.6 Hz), 28.81, 29.03 (2C), 29.05, 34.05, 51.43, 60.28, 107.07 (d, $^2J_{\text{C-F}}$ 28.9 Hz), 120.12 (d, $^4J_{\text{C-F}}$ 9.9 Hz), 138.40 (d, $^3J_{\text{C-F}}$ 14.1 Hz), 166.89, 172.47 (d, $^1J_{\text{C-F}}$ 266.0 Hz), 174.26; $\nu(\text{neat})/\text{cm}^{-1}$ 1739, 1716. [Calc. for $\text{C}_{17}\text{H}_{27}\text{FO}_4$ (M):

314.1886. Found: M⁺, 314.1915]; (Calc. for C₁₇H₂₇FO₄: C, 64.94; H, 8.66. Found: C, 64.97, H, 8.75%).

Methyl (10*E*,12*E*)-10-fluoro-14-oxotetradeca-10,12-dienoate (4f)

R_f 0.53 (hexane-ether 1:1); δ_H(CDCl₃) 1.26-1.38 (10H, m), 1.60-1.63 (4H, m), 2.30 (3H, t, *J* 7.6 Hz), 2.49 (2H, dt, *J* 7.3, ³*J*_{H-F} 23.4 Hz), 3.67 (3H, s), 6.01 [1H, dd, *J* 11.7, ³*J*_{H-F(olefin)} 18.1 Hz], 6.15 (1H, dd, *J* 7.8, 15.1 Hz), 7.15 (1H, dd, *J* 11.7, 15.1 Hz), 9.56 (1H, d, *J* 7.8 Hz); δ_F(CDCl₃) -82.68 [1F, dt, ³*J*_{H-F(olefin)} 18.1, ³*J*_{H-F} 23.4 Hz]; δ_C(CDCl₃) 24.82, 26.19, 28.83, 28.94 (d, ²*J*_{C-F} 24.7 Hz), 29.00 (3C), 34.00, 51.45, 107.73 (d, ²*J*_{C-F} 28.9 Hz), 131.01 (d, ⁴*J*_{C-F} 9.8 Hz), 145.97 (d, ³*J*_{C-F} 14.9 Hz), 170.53 (d, ¹*J*_{C-F} 270.9 Hz), 174.21, 192.89; ν(neat)/cm⁻¹ 1738, 1686; [Calc. for C₁₅H₂₃FO₃ (*M*): 270.1631. Found: M⁺, 270.1636].

Methyl (10*E*,12*E*)-10-fluoro-14-oxopentadeca-10,12-dienoate (4g)

R_f 0.51 (hexane-ether 1:1); δ_H(CDCl₃) 1.26-1.37 (8H, m), 1.54-1.64 (4H, m), 2.26 (3H, s), 2.30 (2H, t, *J* 7.3 Hz), 2.47 (2H, dt, *J* 7.6, ³*J*_{H-F} 23.4 Hz), 3.67 (3H, s), 5.87 [1H, dd, *J* 11.9, ³*J*_{H-F(olefin)} 18.5 Hz], 6.17 (1H, d, *J* 15.4 Hz), 7.18 (1H, dd, *J* 11.9, 15.4 Hz); δ_F(CDCl₃) -85.71 [1F, dt, ³*J*_{H-F(olefin)} 18.5, ³*J*_{H-F} 23.4 Hz]; δ_C(CDCl₃) 24.84, 26.22, 28.11, 28.81, 28.86 (d, ²*J*_{C-F} 28.1 Hz), 29.00 (3C), 34.01, 51.41, 107.44 (d, ²*J*_{C-F} 28.9 Hz), 128.93 (d, ⁴*J*_{C-F} 9.9 Hz), 136.84 (d, ³*J*_{C-F} 14.1 Hz), 170.06 (d, ¹*J*_{C-F} 268.5 Hz), 174.21, 197.55; ν(neat)/cm⁻¹ 1738, 1654; [Calc. for C₁₆H₂₅FO₃ (*M*): 284.1788. Found: M⁺, 284.1809].

Methyl (10*E*,12*E*)-10-fluoro-14-oxo-14-phenyltetradeca-10,12-dienoate (4h)

R_f 0.49 (hexane-ether 1:1); δ_H(CDCl₃) 1.26-1.37 (8H, m), 1.58-1.61 (4H, m), 2.30 (2H, t, *J* 7.6 Hz), 2.52 (2H, dt, *J* 7.6, ³*J*_{H-F} 23.4 Hz), 3.66 (3H, s), 6.02 [1H, dd, *J* 11.9, ³*J*_{H-F(olefin)} 18.3 Hz], 6.99 (1H, d, *J* 14.9 Hz), 7.46-7.58 (4H, m), 7.96 (2H, d, *J* 7.3 Hz); δ_F(CDCl₃) -85.34 [1F, dt, ³*J*_{H-F(olefin)} 18.3, ³*J*_{H-F} 23.4 Hz]; δ_C(CDCl₃) 24.87, 26.33, 28.84, 28.96 (d, ²*J*_{C-F} 24.0 Hz), 29.01 (2C),

29.04, 34.03, 51.41, 107.94 (d, $^2J_{C-F}$ 28.1 Hz), 124.03 (d, $^4J_{C-F}$ 10.7 Hz), 128.30 (2C), 128.56 (2C), 132.71, 138.01, 138.64 (d, $^3J_{C-F}$ 14.1 Hz), 170.88 (d, $^1J_{C-F}$ 268.5 Hz), 174.24, 189.70; $\nu(\text{neat})/\text{cm}^{-1}$ 1736, 1675; [Calc. for $\text{C}_{21}\text{H}_{27}\text{FO}_3$ (M): 346.1937. Found: M^+ , 346.1966]; (Calc. for $\text{C}_{21}\text{H}_{27}\text{FO}_3$: C, 72.81; H, 7.86; F, 5.48. Found: C, 72.75; H, 7.96; F, 5.48%).

Ethyl (2*E*,4*E*)-14-chloro-5-fluorotetradeca-2,4-dienoate (4i)

R_f 0.36 (hexane-ether 10:1); $\delta_H(\text{CDCl}_3)$ 1.28-1.43 (13H, m), 1.54-1.60 (2H, m), 1.73-1.80 (2H, m), 2.46 (2H, dt, J 7.6, $^3J_{H-F}$ 23.4 Hz), 3.53 (2H, t, J 6.8 Hz), 4.21 (2H, q, J 7.1 Hz), 5.85 (1H, d, J 14.9 Hz), 5.87 [1H, dd, J 12.2, $^3J_{H-F(\text{olefin})}$ 18.5 Hz], 7.31 (1H, dd, J 12.2, 14.9 Hz); $\delta_F(\text{CDCl}_3)$ -88.04 [1F, dt, $^3J_{H-F(\text{olefin})}$ 18.5, $^3J_{H-F}$ 23.4 Hz]; $\delta_C(\text{CDCl}_3)$ 14.29, 26.25, 26.81, 28.76 (d, $^2J_{C-F}$ 25.6 Hz), 28.76, 28.81, 29.12, 29.23, 32.58, 45.11, 60.27, 107.07 (d, $^2J_{C-F}$ 29.7 Hz), 120.11 (d, $^4J_{C-F}$ 9.8 Hz), 138.40 (d, $^3J_{C-F}$ 14.1 Hz), 166.88, 169.36 (d, $^1J_{C-F}$ 266.0 Hz); $\nu(\text{neat})/\text{cm}^{-1}$ 1716; [Calc. for $\text{C}_{16}\text{H}_{26}\text{ClFO}_2$ (M): 304.1599. Found: M^+ , 304.1622].

(2*E*,4*E*)-14-Chloro-5-fluorotetradeca-2,4-dienal (4j)

R_f 0.27 (hexane-ether 5:1); $\delta_H(\text{CDCl}_3)$ 1.31-1.44 (10H, m), 1.58-1.64 (2H, m), 1.73-1.80 (2H, m), 2.52 (2H, dt, J 7.5, $^3J_{H-F}$ 22.9 Hz), 3.53 (2H, t, J 11.2 Hz), 6.02 [1H, dd, J 12.0, $^3J_{H-F(\text{olefin})}$ 18.2 Hz], 6.15 (1H, dd, J 7.8, 15.3 Hz), 7.15 (1H, dd, J 12.0, 15.3 Hz), 9.56 (1H, d, J 8.1 Hz); $\delta_F(\text{CDCl}_3)$ -85.69 [1F, dt, $^3J_{H-F(\text{olefin})}$ 18.2, $^3J_{H-F}$ 22.9 Hz]; $\delta_C(\text{CDCl}_3)$ 26.21, 26.77, 28.76, 28.86, 28.94 (d, $^2J_{C-F}$ 25.6 Hz), 29.09, 29.21, 32.54, 45.10, 107.73 (d, $^2J_{C-F}$ 29.7 Hz), 131.00 (d, $^4J_{C-F}$ 9.9 Hz), 145.92 (d, $^3J_{C-F}$ 14.1 Hz), 170.54 (d, $^1J_{C-F}$ 271.0 Hz), 192.84; $\nu(\text{neat})/\text{cm}^{-1}$ 1687; [Calc. for $\text{C}_{14}\text{H}_{22}\text{ClFO}$ (M): 260.1343. Found: M^+ , 260.1339].

(3*E*,5*E*)-15-Chloro-6-fluoropentadeca-3,5-dien-2-one (4k)

R_f 0.24 (hexane-ether 5:1); $\delta_H(\text{CDCl}_3)$ 1.26-1.38 (8H, m), 1.39-1.44 (2H, m), 1.55-1.60 (2H, m), 1.73-1.80 (2H, m), 2.26 (3H, s), 2.47 (2H, dt, J 7.6, $^3J_{H-F}$

23.4 Hz), 3.53 (2H, t, J 6.8 Hz), 5.87 [1H, dd, J 11.9, $^3J_{\text{H-F(olefin)}}$ 18.5 Hz], 6.17 (1H, d, J 15.4 Hz), 7.19 (1H, dd, J 11.9, 15.4 Hz); $\delta_{\text{F}}(\text{CDCl}_3)$ -82.65 [1F, dt, $^3J_{\text{H-F(olefin)}}$ 18.5, $^3J_{\text{H-F}}$ 23.4 Hz]; $\delta_{\text{C}}(\text{CDCl}_3)$ 26.23, 26.78, 28.15, 28.76, 28.82, 28.85 (d, $^2J_{\text{C-F}}$ 25.6 Hz), 29.10, 29.21, 32.56, 45.10, 107.44 (d, $^2J_{\text{C-F}}$ 28.9 Hz), 128.90 (d, $^4J_{\text{C-F}}$ 9.9 Hz), 136.82 (d, $^3J_{\text{C-F}}$ 14.0 Hz), 170.08 (d, $^1J_{\text{C-F}}$ 267.6 Hz), 197.54; $\nu(\text{neat})/\text{cm}^{-1}$ 1652; [Calc. for $\text{C}_{15}\text{H}_{24}\text{ClFO}$ (M): 274.1500. Found: M^+ , 274.1523].

(2*E*,4*E*)-14-Chloro-5-fluoro-1-phenyltetradeca-2,4-dien-1-one (4l)

R_f 0.62 (hexane-AcOEt 5:1); $\delta_{\text{H}}(\text{CDCl}_3)$ 1.30-1.42 (10H, m), 1.54-1.62 (2H, m), 1.73-1.80 (2H, m), 2.52 (2H, dt, J 7.6, $^3J_{\text{H-F}}$ 23.4 Hz), 3.52 (2H, t, J 6.6 Hz), 6.02 [1H, dd, J 11.9, $^3J_{\text{H-F(olefin)}}$ 18.3 Hz], 6.99 (1H, d, J 14.9 Hz), 7.46-7.59 (4H, m), 7.96 (2H, d, J 7.3 Hz); $\delta_{\text{F}}(\text{CDCl}_3)$ -85.36 [1F, dt, $^3J_{\text{H-F(olefin)}}$ 18.3, $^3J_{\text{H-F}}$ 23.4 Hz]; $\delta_{\text{C}}(\text{CDCl}_3)$ 26.33, 26.81, 28.76, 28.85, 28.95 (d, $^2J_{\text{C-F}}$ 24.4 Hz), 29.12, 29.23, 32.58, 45.12, 107.96 (d, $^2J_{\text{C-F}}$ 28.9 Hz), 124.02 (d, $^4J_{\text{C-F}}$ 10.7 Hz), 128.30 (2C), 128.57 (2C), 132.72, 138.01, 138.64 (d, $^3J_{\text{C-F}}$ 14.1 Hz), 170.89 (d, $^1J_{\text{C-F}}$ 268.5 Hz), 189.69; $\nu(\text{neat})/\text{cm}^{-1}$ 1666; [Calc. for $\text{C}_{20}\text{H}_{26}\text{ClFO}$ (M): 336.1656. Found: M^+ , 336.1676]; (Calc. for $\text{C}_{20}\text{H}_{26}\text{ClFO}$: C, 71.31; H, 7.78; Cl, 10.52; F, 5.64. Found: C, 71.31; H, 7.89; Cl, 10.46; F, 5.62%).

(3*E*,5*E*)-7-Cyclohexyl-6-fluorohepta-3,5-dien-2-one (4m)

R_f 0.31 (hexane-ether 5:1); $\delta_{\text{H}}(\text{CDCl}_3)$ 0.93-1.02 (2H, m), 1.10-1.31 (3H, m), 1.60-1.75 (6H, m), 2.26 (3H, s), 2.34 (2H, dd, J 7.1, $^3J_{\text{H-F}}$ 24.6 Hz), 5.92 [1H, dd, J 11.9, $^3J_{\text{H-F(olefin)}}$ 18.5 Hz], 6.16 (1H, d, J 15.4 Hz), 7.16 (1H, dd, J 11.9, 15.4 Hz); $\delta_{\text{F}}(\text{CDCl}_3)$ -82.88 [1F, dt, $^3J_{\text{H-F(olefin)}}$ 18.5, $^3J_{\text{H-F}}$ 24.6 Hz]; $\delta_{\text{C}}(\text{CDCl}_3)$ 26.03 (2C), 26.11, 28.11, 32.89 (2C), 35.54, 36.59 (d, $^2J_{\text{C-F}}$ 24.8 Hz), 108.40 (d, $^2J_{\text{C-F}}$ 28.9 Hz), 128.91 (d, $^4J_{\text{C-F}}$ 9.8 Hz), 137.10 (d, $^3J_{\text{C-F}}$ 13.3 Hz), 169.19 (d, $^1J_{\text{C-F}}$ 267.7 Hz), 197.54; $\nu(\text{neat})/\text{cm}^{-1}$ 1651; [Calc. for $\text{C}_{13}\text{H}_{19}\text{FO}$ (M): 210.1420. Found: M^+ , 210.1409].

(2*E*,4*E*)-6-Cyclohexyl-5-fluoro-1-phenylhexa-2,4-dien-1-one (4n)

R_f 0.51 (hexane-AcOEt 5:1); δ_H(CDCl₃) 0.95-1.04 (2H, m), 1.10-1.30 (3H, m), 1.63-1.76 (6H, m), 2.40 (2H, dd, *J* 7.1, ³*J*_{H-F} 24.9 Hz), 6.07 [1H, dd, *J* 11.9, ³*J*_{H-F(olefin)} 18.5 Hz], 6.98 (1H, d, *J* 14.9 Hz), 7.46-7.58 (4H, m), 7.96 (2H, d, *J* 7.1 Hz); δ_F(CDCl₃) -82.47 [1F, dt, ³*J*_{H-F(olefin)} 18.5, ³*J*_{H-F} 24.9 Hz]; δ_C(CDCl₃) 26.08 (2C), 26.15, 32.92 (2C), 35.67, 36.68 (d, ²*J*_{C-F} 24.8 Hz), 108.94 (d, ²*J*_{C-F} 28.1 Hz), 124.04 (d, ⁴*J*_{C-F} 10.7 Hz), 128.35 (2C), 128.59 (2C), 132.73, 138.08, 138.95 (d, ³*J*_{C-F} 13.3 Hz), 170.06 (d, ¹*J*_{C-F} 268.5 Hz), 189.75; ν(neat)/cm⁻¹ 1666; [Calc. for C₁₈H₂₁FO (*M*): 272.1571. Found: M⁺, 272.1577].

Ethyl (2*E*,4*E*)-5-fluoro-15,15-dimethyl-14-oxohexadeca-2,4-dienoate (4o)

R_f 0.38 (hexane-ether 5:1); δ_H(CDCl₃) 1.13 (9H, s), 1.28-1.31 (11H, m), 1.50-1.58 (4H, m), 2.40-2.50 (4H, m), 4.20 (2H, q, *J* 7.3 Hz), 5.85 (1H, d, *J* 15.1 Hz), 5.86 [1H, dd, *J* 11.9, ³*J*_{H-F(olefin)} 18.3 Hz], 7.31 (1H, dd, *J* 11.9, 15.1 Hz); δ_F(CDCl₃) -87.97 [1F, dt, ³*J*_{H-F(olefin)} 18.3, ³*J*_{H-F} 23.3 Hz]; δ_C(CDCl₃) 14.32, 23.89, 26.30, 26.43 (3C), 28.82 (d, ²*J*_{C-F} 25.6 Hz), 28.89, 29.16, 29.25, 29.32, 36.41, 44.11, 60.32, 107.09 (d, ²*J*_{C-F} 28.9 Hz), 120.11 (d, ⁴*J*_{C-F} 10.7 Hz), 138.48 (d, ³*J*_{C-F} 13.3 Hz), 166.96, 169.44 (d, ¹*J*_{C-F} 266.0 Hz), 216.17; ν(neat)/cm⁻¹ 1708, 1661; [Calc. for C₂₀H₃₃FO₃ (*M*): 340.2405. Found: M⁺, 340.2408]; (Calc. for C₂₀H₃₃FO₃: C, 70.55; H, 9.77. Found: C, 70.47; H, 9.70%).

(2*E*,4*E*)-5-Fluoro-15,15-dimethyl-14-oxohexadeca-2,4-dienal (4p)

R_f 0.60 (hexane-ether 1:1); δ_H(CDCl₃) 1.13 (9H, s), 1.30-1.33 (8H, m), 1.51-1.65 (4H, m), 2.42-2.55 (4H, m), 6.01 [1H, dd, *J* 11.9, ³*J*_{H-F(olefin)} 18.1 Hz], 6.15 (1H, dd, *J* 7.8, 15.1 Hz), 7.17 (1H, dd, *J* 11.9, 15.1 Hz), 9.56 (1H, d, *J* 7.8 Hz); δ_F(CDCl₃) -82.64 [1F, dt, ³*J*_{H-F(olefin)} 18.1, ³*J*_{H-F} 24.8 Hz]; δ_C(CDCl₃) 23.80, 26.20, 26.38 (3C), 28.86, 28.92 (d, ²*J*_{C-F} 24.0 Hz), 29.04, 29.18, 29.28, 36.33, 44.06, 107.72 (d, ²*J*_{C-F} 28.9 Hz), 130.99 (d, ⁴*J*_{C-F} 9.9 Hz), 145.97 (d, ³*J*_{C-F} 14.1 Hz), 170.58 (d, ¹*J*_{C-F} 271.0 Hz), 192.88, 216.03; ν(neat)/cm⁻¹ 1703, 1653; [Calc. for C₁₈H₂₉FO₂ (*M*): 296.2151. Found: M⁺, 296.2140].

(3*E*,5*E*)-6-Fluoro-16,16-dimethylheptadeca-3,5-dien-2,15-dione (4q)

R_f 0.58 (hexane-ether 1:1); δ_H(CDCl₃) 1.13 (9H, s), 1.29-1.31 (8H, m), 1.50-1.60 (4H, m), 2.26 (3H, s), 2.42-2.51 (4H, m), 5.87 [1H, dd, *J* 11.9, ³*J*_{H-F(olefin)} 18.5 Hz], 6.17 (1H, d, *J* 15.3 Hz), 7.19 (1H, dd, *J* 11.9, 15.3 Hz); δ_F(CDCl₃) -85.64 [1F, dt, ³*J*_{H-F(olefin)} 18.5, ³*J*_{H-F} 24.1 Hz]; δ_C(CDCl₃) 23.82, 26.24, 26.38 (3C), 28.10, 28.84, 28.85 (d, ²*J*_{C-F} 25.6 Hz), 29.08, 29.19, 29.27, 36.34, 44.05, 107.42 (d, ²*J*_{C-F} 28.9 Hz), 128.93 (d, ⁴*J*_{C-F} 10.7 Hz), 136.87 (d, ³*J*_{C-F} 13.3 Hz), 170.09 (d, ¹*J*_{C-F} 267.7 Hz), 197.56, 216.02; ν(neat)/cm⁻¹ 1704, 1652; [Calc. for C₁₉H₃₁FO₂ (*M*): 310.2308. Found: M⁺, 310.2306].

(2*E*,4*E*)-5-Fluoro-15,15-dimethyl-1-phenylhexadeca-2,4-dien-1,14-dione (4r)

R_f 0.62 (hexane-ether 1:1); δ_H(CDCl₃) 1.13 (9H, s), 1.29-1.32 (8H, m), 1.50-1.61 (4H, m), 2.44-2.57 (4H, m), 6.02 [1H, dd, *J* 11.9, ³*J*_{H-F(olefin)} 18.3 Hz], 6.99 (1H, d, *J* 14.9 Hz), 7.46-7.59 (4H, m), 7.96 (2H, d, *J* 7.1 Hz); δ_F(CDCl₃) -85.31 [1F, dt, ³*J*_{H-F(olefin)} 18.3, ³*J*_{H-F} 23.3 Hz]; δ_C(CDCl₃) 23.89, 26.38, 26.42 (3C), 28.92, 29.00 (d, ²*J*_{C-F} 25.5 Hz), 29.16, 29.24, 29.32, 36.40, 44.09, 107.97 (d, ²*J*_{C-F} 28.9 Hz), 124.05 (d, ⁴*J*_{C-F} 10.7 Hz), 128.34 (2C), 128.60 (2C), 132.75, 138.07, 138.71 (d, ³*J*_{C-F} 13.3 Hz), 170.96 (d, ¹*J*_{C-F} 268.5 Hz), 189.75, 216.09; ν(neat)/cm⁻¹ 1698, 1670; [Calc. for C₂₄H₃₃FO₂ (*M*): 372.2456. Found: M⁺, 372.2452]; (Calc. for C₂₄H₃₃FO₂: C, 77.38; H, 8.93; F, 5.10. Found: C, 77.34; H, 8.85; F, 5.34%).

General procedure for (*E*)-4-fluoro-1,3-dienes (5)

To a DMF solution (20 mL) of Bn(PPh₃)₂PdCl, prepared *in situ* by the addition of benzyl chloride (12.6 mg, 0.1 mmol) to a DMF solution (20 mL) of Pd(PPh₃)₄ (116 mg, 0.1 mmol),¹⁵ a DMF solution (4 mL) of the alkenyliodonium salt (**2**) prepared as already described was added at room temperature. After the addition of tributylvinylstannane (695 mg, 2.2 mmol), the reaction mixture was stirred at room temperature for 18 h and then poured into saturated aqueous NH₄Cl. After extraction with ether,

the organic phase was dried over MgSO_4 and concentrated under reduced pressure. The (*E*)-4-fluoro-1,3-dienes (**5**) and *p*-vinyltoluene (**10**) were isolated by column chromatography (silica gel/hexane-ether).

Methyl (10*E*,12*E*)-10-fluorotrideca-10,12-dienoate (5a)

$\delta_{\text{H}}(\text{CDCl}_3)$ 1.30 (8H, s), 1.50-1.63 (4H, m), 2.30 (2H, t, J 7.8 Hz), 2.33 (2H, dt, J 7.3, $^3J_{\text{H-F}}$ 23.9 Hz), 3.67 (3H, s), 4.99 (1H, d, J 10.2 Hz), 5.13 (1H, d, J 16.8 Hz), 5.75 [1H, dd, J 11.2, $^3J_{\text{H-F(olefin)}}$ 20.0 Hz], 6.26 (1H, dd, J 11.2, 16.8 Hz); $\delta_{\text{F}}(\text{CDCl}_3)$ -101.05 [1F, dt, $^3J_{\text{H-F(olefin)}}$ 20.0, $^3J_{\text{H-F}}$ 23.9 Hz]; $\nu(\text{neat})/\text{cm}^{-1}$ 1740; [Calc. for $\text{C}_{14}\text{H}_{23}\text{FO}_2$ (M): 242.1683, Found: M^+ , 242.1697].

(*E*)-13-Chloro-4-fluorotrideca-1,3-diene (5b)

$\delta_{\text{H}}(\text{CDCl}_3)$ 1.30 (8H, s), 1.40-1.44 (2H, m), 1.50-1.56 (2H, m), 1.71-1.80 (2H, m), 2.34 (2H, dt, J 7.3, $^3J_{\text{H-F}}$ 23.7 Hz), 3.53 (2H, t, J 6.8 Hz), 5.00 (1H, d, J 10.2 Hz), 5.14 (1H, d, J 16.6 Hz), 5.78 [1H, dd, J 11.2, $^3J_{\text{H-F(olefin)}}$ 19.7 Hz], 6.27 (1H, dt, J 11.2, J 16.6 Hz); $\delta_{\text{F}}(\text{CDCl}_3)$ -101.05 [1F, dt, $^3J_{\text{H-F(olefin)}}$ 19.7, $^3J_{\text{H-F}}$ 23.7 Hz]; [Calc. for $\text{C}_{13}\text{H}_{22}\text{ClF}$ (M): 232.1396, Found: M^+ , 232.1382].

(*E*)-5-Cyclohexyl-4-fluoropenta-1,3-diene (5c)

$\delta_{\text{H}}(\text{CDCl}_3)$ 0.87-0.99 (2H, m), 1.09-1.30 (3H, m), 1.54-1.75 (6H, m), 2.22 (2H, dd, J 7.2, $^3J_{\text{H-F}}$ 24.4 Hz), 4.98 (1H, d, J 10.4 Hz), 5.12 (1H, d, J 16.8 Hz), 5.80 [1H, dd, J 11.2, $^3J_{\text{H-F(olefin)}}$ 20.0 Hz], 6.25 (1H, dt, J 11.2, 16.8 Hz); $\delta_{\text{F}}(\text{CDCl}_3)$ -98.09 [1F, dt, $^3J_{\text{H-F(olefin)}}$ 20.0, $^3J_{\text{H-F}}$ 24.4 Hz]; [Calc. for $\text{C}_{11}\text{H}_{17}\text{F}$ (M): 168.1315, Found: M^+ , 168.1314].

(*E*)-2,2-Dimethyl-12-fluoropentadeca-12,14-dien-3-one (5d)

$\delta_{\text{H}}(\text{CDCl}_3)$ 1.13 (9H, s), 1.29 (8H, s), 1.54-1.58 (4H, m), 2.32 (2H, dt, J 7.3, $^3J_{\text{H-F}}$ 23.7 Hz), 2.46 (2H, t, J 7.3 Hz), 4.99 (1H, d, J 10.3 Hz), 5.13 (1H, d, J 16.5 Hz), 5.75 [1H, dd, J 11.2, $^3J_{\text{H-F(olefin)}}$ 20.0 Hz], 6.27 (1H, dt, J 11.2, 16.5 Hz); $\delta_{\text{F}}(\text{CDCl}_3)$ -101.02 [1F, dt, $^3J_{\text{H-F(olefin)}}$ 20.0, $^3J_{\text{H-F}}$ 23.7 Hz]; $\nu(\text{neat})/\text{cm}^{-1}$ 1706; [Calc. for $\text{C}_{17}\text{H}_{29}\text{FO}$ (M): 268.2204, Found: M^+ , 268.2185].

(E)-4-Fluorotetradeca-1,3-diene (5e)

$\delta_{\text{H}}(\text{CDCl}_3)$ 0.88 (3H, t, J 7.3 Hz), 1.26 (14H, s), 1.50-1.58 (2H, m), 2.34 (2H, dt, J 7.6, $^3J_{\text{H-F}}$ 23.6 Hz), 4.99 (1H, d, J 10.2 Hz), 5.13 (1H, d, J 16.8 Hz), 5.75 [1H, dd, J 11.2, $^3J_{\text{H-F(olefin)}}$ 20.0 Hz], 6.27 (1H, dt, J 11.2, 16.8 Hz); $\delta_{\text{F}}(\text{CDCl}_3)$ -101.02 [1F, dt, $^3J_{\text{H-F(olefin)}}$ 20.0, $^3J_{\text{H-F}}$ 23.6 Hz]; [Calc. for $\text{C}_{14}\text{H}_{25}\text{F}$ (M): 212.1942, Found: M^+ , 212.1938].

(1E,3E)-4-Fluoro-1-phenyltetradeca-1,3-diene (5f)

$\delta_{\text{H}}(\text{CDCl}_3)$ 0.87 (3H, t, J 7.1 Hz), 1.26 (14H, s), 1.57-1.62 (2H, m), 2.44 (2H, dt, J 7.3, $^3J_{\text{H-F}}$ 23.4 Hz), 5.88 [1H, dd, J 11.2, $^3J_{\text{H-F(olefin)}}$ 19.7 Hz], 6.46 (1H, d, J 15.6 Hz), 6.65 (1H, dd, J 11.2, 15.6 Hz), 7.19-7.38 (5H, m); $\delta_{\text{F}}(\text{CDCl}_3)$ -99.49 [1F, dt, $^3J_{\text{H-F(olefin)}}$ 19.7, $^3J_{\text{H-F}}$ 23.4 Hz]; [Calc. for $\text{C}_{20}\text{H}_{29}\text{F}$ (M): 288.2320, Found: M^+ , 288.2248].

Methyl (9E,11E)-9-fluoro-13-oxooctadeca-9,11-dienoate (7)

$\delta_{\text{H}}(\text{CDCl}_3)$ 0.90 (3H, t, J 7.1 Hz), 1.27-1.34 (10H, m), 1.54-1.66 (6H, m), 2.30 (2H, t, J 7.6 Hz), 2.46 (2H, dt, J 7.6, $^3J_{\text{H-F}}$ 23.4 Hz), 2.51 (2H, t, J 7.6 Hz), 3.67 (3H, s), 5.86 [1H, dd, J 11.9, $^3J_{\text{H-F(olefin)}}$ 18.5 Hz], 6.19 (1H, d, J 15.1 Hz), 7.22 (1H, dd, J 11.9, 15.1 Hz); $\delta_{\text{F}}(\text{CDCl}_3)$ -86.35 [1F, dt, $^3J_{\text{H-F(olefin)}}$ 18.5, $^3J_{\text{H-F}}$ 23.4 Hz]; $\nu(\text{neat})/\text{cm}^{-1}$ 1739, 1691; [Calc. for $\text{C}_{19}\text{H}_{31}\text{FO}_3$ (M): 326.2249, Found: M^+ , 326.2272].

Methyl ester of 9-fluoro 13 HODE (8)

To a MeOH solution (2.5 mL) of **7** (326 mg, 1 mmol) and $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ (372 mg, 1 mmol) was added NaBH_4 (38 mg, 1 mmol) at room temperature with stirring. After 3 minutes, the reaction mixture was poured into water (10 mL) and extracted with diethyl ether (10 mL \times 3). The organic phase was dried over MgSO_4 and concentrated under reduced pressure. The desired methyl ester of 9-fluoro 13 HODE (**7**) (328 mg, 1 mmol) was obtained without further purification.

$\delta_{\text{H}}(\text{CDCl}_3)$ 0.89 (3H, t, J 6.8 Hz), 1.30-1.32 (14H, m), 1.49-1.64 (5H, m), 2.30

(2H, t, J 7.6 Hz), 2.34 (2H, dt, J 7.1, $^3J_{\text{H-F}}$ 23.9 Hz), 3.67 (3H, s), 4.11-4.16 (1H, m), 5.61 (1H, dd, J 6.8, 15.1 Hz), 5.72 [1H, dd, J 11.2, $^3J_{\text{H-F(olefin)}}$ 19.7 Hz], 6.13 (1H, dd, J 11.2, 15.1 Hz); $\delta_{\text{F}}(\text{CDCl}_3)$ -101.18 [1F, dt, $^3J_{\text{H-F(olefin)}}$ 19.7, $^3J_{\text{H-F}}$ 23.9 Hz]; [Calc. for $\text{C}_{19}\text{H}_{33}\text{FO}_3$ (M): 328.2414, Found: M^+ , 328.2432].

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Chapter 4

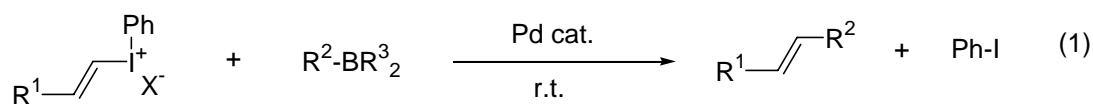
Regio- and Stereoselective Synthesis of Fluoroalkenes and Fluoroalkadienes via Pd-Catalyzed Coupling Reaction of (*E*)-2-Fluoro-1-iodoalk-1-enes with Organoboranes

Abstract

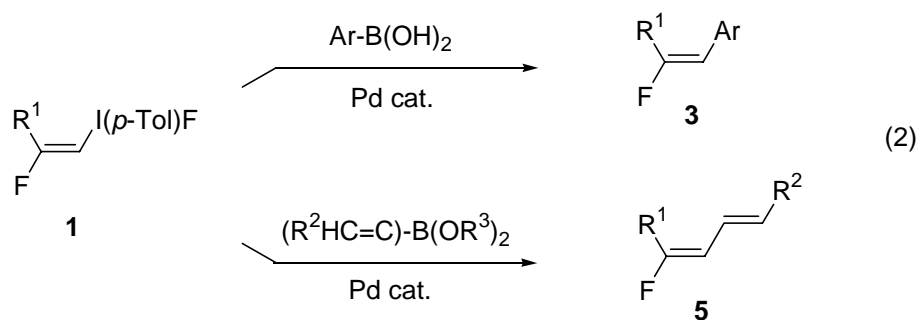
The cross-coupling reactions of (*E*)-2-fluoro-1-iodoalk-1-enes with arylboronic acids were carried out in the presence of a Pd catalyst to give (*E*)- β -fluorostyrene derivatives stereoselectively in good yields. Similarly, various (*E,E*)-fluoroalkadienes were stereoselectively obtained by the reactions of (*E*)-fluoroiodoalkenes with (*E*)-alkenylboranes.

Introduction

Fluoroalkene synthesis has received the considerable attention of biological and medicinal chemists because the introduction of a fluorine atom into the double bond of a biologically active compound can dramatically enhance its bioactivity.^{1,2} When a fluorinated analog of a bioactive compound having a fluorine atom on its double bond is synthesized, regio- and stereoselective introduction of a fluorine atom is important because the bioactivity strongly depends on the position and stereochemistry of the fluorine atom.³ The most popular method for the fluoroalkene synthesis is the Horner-Wadsworth-Emmons reaction using fluoroorganophosphonates with carbonyl compounds; however, a mixture of stereoisomers is generally formed.² Pd-catalyzed cross-coupling reactions using alkenyl halides or metals has been used in synthesis of an alkene function of a natural compound. However, the cross-coupling method has not been well developed for the fluoroalkene synthesis because the stereoselective synthesis of fluoroalkenyl halides or metals is difficult. As shown in Chapter 1, the author succeeded in the stereo- and regioselective synthesis of (*E*)-2-fluoroalk-1-enyl(4-methylphenyl)iodonium fluorides (**1**) and (*E*)-2-fluoro-1-iodoalk-1-enes (**2**).^{4a} In Chapters 2 and 3, the fluoroalkenyliodonium salts (**1**) were stereoselectively converted to (*E*)- β -fluoro- α,β -unsaturated esters^{4b} and (*E,E*)- δ -fluoro- $\alpha,\beta,\gamma,\delta$ -unsaturated carbonyl compounds^{4c} by Pd-catalyzed cross-coupling reactions. Recently, Kang *et al.* reported that the Pd-catalyzed cross-coupling reaction between alkenyliodonium salts with organoboranes (Suzuki-Miyaura reaction)⁵ proceeded at room temperature to give the coupling products [Eq. (1)].^{6b,c}



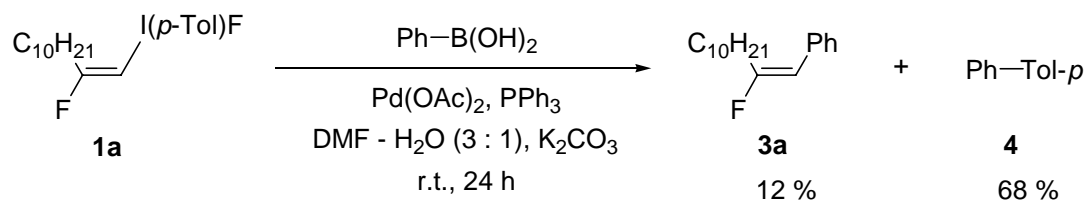
As organoboranes are readily obtainable using hydroboration or diboration reactions,⁷ and a number of them are commercially available, the author attempted the cross-coupling reaction using **1** with organoboranes [Eq. (2)].



Results and Discussion

Cross-coupling reaction of (*E*)-2-fluoroalk-1-enyl(4-methylphenyl)iodonium fluorides (**1**) with organoboranes

Initially, the cross-coupling reaction of (*E*)-2-fluorododec-1-enyl(4-methylphenyl)iodonium fluoride (**1a**) with phenylboronic acid was carried out in the presence of Pd(OAc)₂, PPh₃ and K₂CO₃ in DMF–water (3 : 1) (Scheme 1).⁶ The coupling reaction proceeded at room temperature; however, (*E*)-2-fluoro-1-phenyldodec-1-ene (**3a**) was obtained only in 12% yield along with 4-phenyltoluene (**4**) (68%) generated by the coupling reaction between the tolyl group on **1a** and phenylboronic acid.⁸ In the Heck reaction, the Stille reaction and methoxycarbonylation using **1**, the coupling reaction preferentially took place at the alkenyl part of **1** and a by-product derived from the reaction at the tolyl part such as **4** was scarcely obtained. In order to suppress the formation of **4**, the author re-examined his reaction conditions, but the result could not be improved.



Scheme 1.

Kang *et al.* reported that in the cross-coupling reaction using (*E*)- β -styryl(phenyl)iodonium salt with phenylboronic acid, the formation of biphenyl was not observed.^{6b,c} Therefore, in the reaction of **1a** with phenylboronic acid, the alkyl group at the *cis*-position to iodine⁹ or the fluorine atom on the double bond retarded the oxidative addition of the Pd catalyst to the iodine–alkenyl bond and the selective formation of **3a** was disturbed.¹⁰ Consequently, the author gave up the selective synthesis of fluoroalkenes using **1**, and examined the coupling reaction using

(*E*)-2-fluoro-1-iodoalk-1-enes (**2**) which can be prepared from **1** as shown in Chapter 1.^{4a}

Cross-coupling reaction of (*E*)-2-fluoro-1-iodoalk-1-enes (**2**) with arylboronic acids

The cross-coupling reaction of (*E*)-2-fluoro-1-iodododec-1-ene (**2a**) with phenylboronic acid was examined to find a suitable catalyst (Table 1).

Table 1. Cross-coupling reaction of **2a** with phenylboronic acid^a

Entry	Catalyst	Time / h	Yield / % ^b
1	Pd(PPh ₃) ₄	12	65
2	Pd(PPh ₃) ₂ Cl ₂	12	56
3	Pd(OAc) ₂ + DPPP	5	48
4	Pd(OAc) ₂ + DPPF	5	70
5	Pd(OAc) ₂ + BINAP	5	85

^a The reaction was carried out using **2a** (0.5 mmol), phenylboronic acid (1 mmol), Pd cat. (5 mol %), ligand (5 mol %), aq. 2M-K₂CO₃ (0.5 mL) and benzene (5 mL).

^b Isolated yield based on **2a**.

When Pd(PPh₃)₄ or Pd(PPh₃)₂Cl₂, a common catalyst in the Suzuki–Miyaura reaction,⁶ was used with K₂CO₃ in benzene under reflux, it took about 12 h to consume **2a** completely and the desired coupling product **3a** was obtained in moderate yield (Entries 1 and 2). As **2a** can be unstable under the reaction conditions, it was necessary to complete the reaction in a shorter period to obtain **3a** in good yield. Fortunately, the reaction was found to be accelerated by using Pd(OAc)₂ with bidentate ligands, such as 1,3-bis(diphenylphosphino)propane (DPPP), bis(diphenylphosphino)ferrocene (DPPF) and 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP), and completed in 5 h (Entries 3–5).¹¹ Finally, the author succeeded in obtaining **3a** in 85% yield by using BINAP as a

ligand (Entry 5). Although the coupling reaction using fluoroiodoalkene (**2a**) required a longer reaction time and higher temperature compared with that using fluoroalkenyliodonium salt (**1a**), the yield of the desired coupling product **3a** was dramatically increased. Under these reaction conditions, the cross-coupling reaction between a variety of (*E*)-2-fluoro-1-iodoalk-1-enes (**2**) and arylboronic acids took place to give (*E*)-fluoroalkenes in 74–94% yield and with more than 98% stereoselectivity (Table 2).

Table 2. Cross-coupling reaction of **2** with arylboronic acid

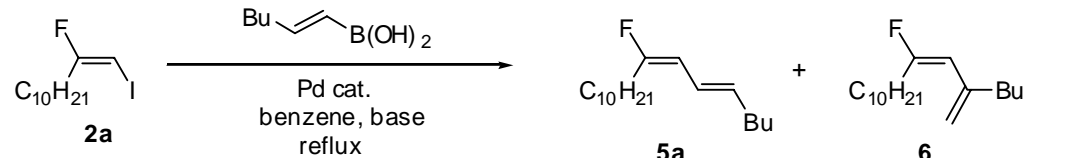
Entry	Fluoriodoalkene 2	Arylboronic acid	Product	Yield / % ^a
1				85
2	2a			92
3	2a			94
4				93
5				77
6				90
7				74

^a Isolated yield based on **2**.

Cross-coupling reaction of (*E*)-2-fluoro-1-iodoalk-1-enes (**2**) with (*E*)-alk-1-enylboronic acids or -boronates

The coupling reaction of **2** with (*E*)-alk-1-enylboronic acids or -boronates was examined to obtain the fluorinated conjugated dienes (**5**). When the coupling reaction between **2a** and (*E*)-hex-1-enylboronic acid was carried out under the same conditions as optimized in Table 1, the desired (*5E,7E*)-8-fluorooctadeca-5,7-diene (**5a**) was obtained in 73% yield along with 9% of its isomer **6** (Table 3).

Table 3. Cross-coupling reaction of **2a** with (*E*)-hex-1-enylboronic acid



The reaction scheme shows the cross-coupling of **2a** (C₁₀H₂₁F-I) with (*E*)-hex-1-enylboronic acid (Bu-CH=CH-B(OH)₂) using a Pd catalyst in benzene with a base under reflux. The products are (*5E,7E*)-8-fluorooctadeca-5,7-diene (**5a**) and its isomer **6**.

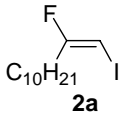
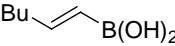
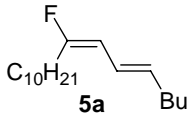
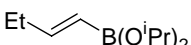
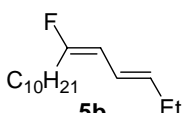
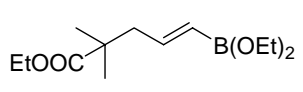
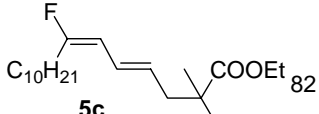
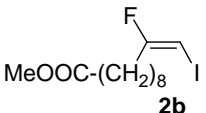
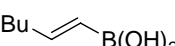
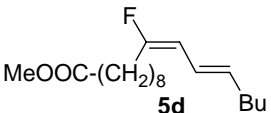
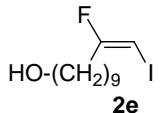
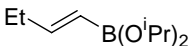
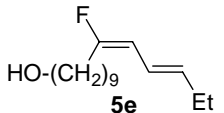
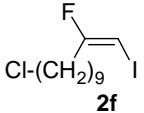
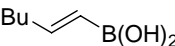
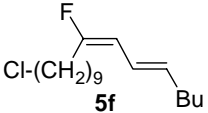
Entry	Catalyst	Base	Time / h	Yield / % ^a	
				5a	6
1	Pd(OAc) ₂ + BINAP	K ₂ CO ₃	3.5	73	9
2	Pd(OAc) ₂ + BINAP	KOH	2	89	1
3	Pd(OAc) ₂ + 2BINAP	KOH	2	87	trace

^a Isolated yield. The ratio of **5a** and **6** was determined by ¹H-NMR.

Owing to the low nucleophilicity of an alkenylboronic acid compared with an aryl derivative, the transmetallation step of the Pd catalyst was slow and a Heck-type side reaction took place competitively to give **6**.¹² In order to accelerate the transmetallation step and suppress the formation of **6**, a stronger base, KOH, was used instead of K₂CO₃. As expected, the reaction completed in a shorter reaction time and the formation of **6** could be suppressed. Finally, the author succeeded in synthesizing **5a** in 87% yield without the formation of **6** by using Pd(OAc)₂, BINAP and KOH. Under these reaction conditions, various fluoroalkadienes (**5**) could be prepared from **2** and (*E*)-alk-1-enylboranes with more than 98% stereoselectivity in 67–87% yield (Table 4). When diisopropyl (*E*)-but-1-enylboronate was used, the reaction proceeded slowly

and the yield of **5** decreased due to the high solubility of diisopropyl (*E*)-but-1-enylboronate in water. This problem was overcome by using dioxane as solvent instead of benzene (Entries 2 and 5).

Table 4. Stereoselective synthesis of fluoroalkadienes (**5**)

Entry	Fluoroiodoalkene 2	Alkenylboronic acid	Product	Yield / % ^a
1				87
2	2a			67 ^b
3	2a			82
4				85
5				67 ^b
6				80

^a Isolated yield based on **2**.

^b The reaction was carried out in dioxane at 70 °C.

Conclusion

(*E*)-Fluoroalkenes and (*E,E*)-fluoroalkadienes having various functionalities were synthesized stereoselectively by the cross-coupling reaction between (*E*)-2-fluoro-1-iodoalk-1-enes and organoboranes.

Experimental

General

IR spectra were recorded using a JASCO FT/IR-410. ^1H NMR (400 MHz), ^{19}F NMR (376 MHz) and ^{13}C -NMR (100 MHz) spectra were recorded in CDCl_3 on a JEOL JNM-A400II FT NMR and chemical shifts, δ , are referred to TMS (^1H , ^{13}C) and CFCl_3 (^{19}F). EI low- and high-resolution mass spectra were measured on a JEOL JMS-700TZ, JMS-FABmate or JMS-HX110. Elemental microanalyses were done using a Yanagimoto CHN Corder MT-5. For column chromatography, Merck silica gel 7734 was used, and for analytical TLC, Merck silica gel 5715 was used. 11-Acetoxyundec-1-yne^{13a} was prepared from undec-10-yn-1-ol^{13b} which was in turn prepared from undec-10-en-1-ol. PdCl_2 , $\text{Pd}(\text{PPh}_3)_4$, $\text{Pd}(\text{OAc})_2$, PPh_3 , and phenylboronic acid were purchased from Tokyo Kasei Co., Ltd., and used without further purification. DPPP, DPPF and BINAP were purchased from Kanto Kagaku Co., Ltd., and used without further purification. *o*-Tolylboronic acid,¹⁴ 1-naphthylboronic acid,¹⁴ (*E*)-hex-1-enylboronic acid,¹⁵ diisopropyl (*E*)-but-1-enylboronate¹⁶ and diethyl [(*E*)-4-ethoxycarbonyl-4-methylpent-1-enyl]boronate²⁶ were prepared according to the literature. Preparation of $\text{Et}_3\text{N}\cdot 5\text{HF}$, dodec-1-yne, 3-cyclohexylprop-1-yne, 11-chloroundec-1-yne, methyl undec-10-ynoate and 2,2-dimethyltridec-12-yn-3-one were shown in Chapter 1. The procedures for the preparation of (*E*)-fluoroalkenyliodonium salts (**1**) and (*E*)-2-fluoro-1-iodoalk-1-enes (**2**) were also shown in Chapter 1.³ Preparation of methyl dec-9-ynoate was described in Chapter 3.

For the spectrum information of (*E*)-2-fluoro-1-iodododec-1-ene (**2a**), methyl (*E*)-10-fluoro-11-iodoundec-10-enoate (**2b**), (*E*)-12-fluoro-13-iodo-2,2-dimethyltridec-12-en-3-one (**2c**), (*E*)-10-fluoro-11-iodoundec-10-en-1-ol (**2e**) and (*E*)-11-chloro-2-fluoro-1-iodoundec-1-ene (**2f**), see Chapter 1.

(*E*)-11-Acetoxy-2-fluoro-1-iodoundec-1-ene (2d).

$\delta_{\text{H}}(\text{CDCl}_3)$ 1.28–1.39 (10H, m), 1.53–1.64 (4H, m), 2.05 (3H, s, MeCO), 2.50 (2H, dt, $^3J_{\text{H-F}}$ 22.7, J 7.3 Hz, 3-H), 4.05 (2H, t, J 6.8 Hz, 11-H), 5.67 [1H, d, $^3J_{\text{H-F(olefin)}}$ 17.8 Hz, 1-H]; $\delta_{\text{C}}(\text{CDCl}_3)$ 21.03, 25.69, 25.88, 28.59, 28.67, 29.28 (2C), 29.31, 30.92 (d, $^2J_{\text{C-F}}$ 26.4 Hz, 3-C), 54.73 (d, $^2J_{\text{C-F}}$ 39.7 Hz, 1-C), 64.62, 164.16 (d, $^1J_{\text{C-F}}$ 264.4 Hz, 2-C), 171.22; $\delta_{\text{F}}(\text{CDCl}_3)$ 82.48 [1F, dt, $^3J_{\text{H-F}}$ 22.7, $^3J_{\text{H-F(olefin)}}$ 17.8 Hz]; $\nu(\text{neat})/\text{cm}^{-1}$ 3077, 2929, 2856, 1740, 1650, 1464, 1430, 1388, 1365, 1240, 1125, 1079, 1038, 871, 772, 714; m/z 337 ($M^+ - \text{F}$, 3%), 324 (3), 311 (2), 254 (10), 229 (14), 221 (7), 209 (4), 198 (79), 185 (14), 169 (3), 149 (66), 121 (10), 107 (25), 93 (31), 69 (44), 55 (67), 43 (100) [Calc. for $\text{C}_{13}\text{H}_{22}\text{IO}_2$ ($M - \text{F}$): 337.0649. Found: $M^+ - \text{F}$, 337.0665].

Cross-coupling reaction of (*E*)-2-fluorododec-1-enyl(4-methylphenyl)iodonium salt (1a) with phenylboronic acid

(*E*)-2-Fluorododec-1-enyl(4-methylphenyl)iodonium salt (**1a**), prepared from dodec-1-yne (83 mg, 0.5 mmol),³ was dissolved in a 3 : 1 mixture of DMF and water (5 mL). To this solution, were added K_2CO_3 (346 mg, 2.5 mmol), PPh_3 (262 mg, 0.1 mmol), $\text{Pd}(\text{OAc})_2$ (225 mg, 0.1 mmol) and phenylboronic acid (91 mg, 0.75 mmol) sequentially. The reaction mixture was stirred for 24 h at room temperature. The resulting solution was poured into saturated aq. NH_4Cl (20 mL) and extracted with diethyl ether (10 mL \times 3). The combined organic phase was washed with water (30 mL) and dried over MgSO_4 . After the MgSO_4 was removed by filtration, the solvent was removed by evaporation. The desired product **3a** was isolated in 12% yield by column chromatography (silica gel; hexane–diethyl ether). 4-Phenyltoluene (**4**) was obtained as a mixture with biphenyl, and the yield of **4** was determined by gas chromatography.

General procedure for (*E*)-fluoroalkenes (3)

To a mixture of benzene (5 mL) and 0.5 mL of 2 M aq. K_2CO_3 (1.0 mmol), were added $\text{Pd}(\text{OAc})_2$ (5.6 mg, 0.025 mmol) and (*S*)-(-)-BINAP (15.6

mg, 0.025 mmol). After the complete replacement of atmosphere in the flask with N₂, an (*E*)-2-fluoro-1-iodoalk-1-ene (**2**) (0.5 mmol) and arylboronic acid (1.0 mmol) were added. Then the reaction mixture was stirred under reflux for 5 h and then cooled to room temperature. The resulting solution was poured into saturated aq. NH₄Cl (20 mL) and extracted with diethyl ether (10 mL × 3). The combined organic phase was washed with water (30 mL) and dried over MgSO₄. After the MgSO₄ was removed by filtration, the solvent was removed by evaporation. The desired product **3** was isolated in 12% yield by column chromatography (silica gel; hexane–diethyl ether).

(*E*)-2-Fluoro-1-phenyldodec-1-ene (3a).

$\delta_{\text{H}}(\text{CDCl}_3)$ 0.88 (3H, t, J 7.0 Hz, 12-H), 1.25–1.33 (14H, m), 1.57–1.65 (2H, m, 4-H), 2.43 (2H, dt, $^3J_{\text{H-F}}$ 23.4, J 7.6 Hz, 3-H), 6.18 [1H, d, $^3J_{\text{H-F(olefin)}}$ 21.9 Hz, 1-H], 7.18–7.34 (5H, m, Ph); $\delta_{\text{F}}(\text{CDCl}_3)$ 99.03 (1F, m); $\delta_{\text{C}}(\text{CDCl}_3)$ 14.11, 22.67, 26.37, 28.96 (d, $^2J_{\text{C-F}}$ 26.4 Hz, 3-C), 29.14, 29.31 (2C), 29.50, 29.56, 31.88, 108.02 (d, $^2J_{\text{C-F}}$ 28.9 Hz, 1-C), 126.53 (2C), 128.40 (3C), 134.41 (d, $^3J_{\text{C-F}}$ 14.1 Hz, *ipso*-Ph), 162.77 (d, $^1J_{\text{C-F}}$ 252.7 Hz, 2-C); $\nu(\text{neat})/\text{cm}^{-1}$ 3084, 3059, 3027, 2955, 2926, 2854, 1682, 1601, 1496, 1466, 1377, 1225, 1142, 1095, 913, 885, 844, 747, 697; m/z 262 (M⁺, 100%), 135 (53), 122 (18), 115 (18), 104 (8), 91 (12), 57 (7), 43 (13) [Calc. for C₁₈H₂₇F (*M*): 262.2097. Found: M⁺, 262.2093] (Calc. for C₁₈H₂₇F: C, 82.39; H, 10.37. Found: C, 82.58; H, 10.53%).

(*E*)-2-Fluoro-1-(2-methylphenyl)dodec-1-ene (3b).

$\delta_{\text{H}}(\text{CDCl}_3)$ 0.88 (3H, t, J 6.9 Hz, 12-H), 1.28–1.33 (14H, m), 1.52–1.60 (2H, m, 4-H), 2.25 (3H, s, C₆H₄Me), 2.30 (2H, dt, $^3J_{\text{H-F}}$ 22.9, J 7.6 Hz, 3-H), 6.14 [1H, d, $^3J_{\text{H-F(olefin)}}$ 21.2 Hz, 1-H], 7.10–7.18 (4H, m, ArH); $\delta_{\text{F}}(\text{CDCl}_3)$ -101.46 (1F, m); $\delta_{\text{C}}(\text{CDCl}_3)$ 14.11, 20.07, 22.68, 26.29, 28.56 (d, $^2J_{\text{C-F}}$ 27.2 Hz, 3-C), 29.02, 29.27, 29.31, 29.52, 29.57, 31.90, 106.62 (d, $^2J_{\text{C-F}}$ 27.2 Hz, 1-C), 125.71, 127.07, 129.03, 129.78, 133.45 (d, $^3J_{\text{C-F}}$ 13.3 Hz, *ipso*-Ar), 136.85,

162.36 (d, $^1J_{C-F}$ 252.8 Hz, 2-C); $\nu(\text{neat})/\text{cm}^{-1}$ 3106, 3066, 3021, 2956, 2925, 2854, 1684, 1603, 1484, 1459, 1379, 1233, 1195, 1143, 1095, 885, 845, 788, 746, 721; m/z 276 (M^+ , 100%), 149 (93), 134 (20), 129 (31), 115 (18), 105 (23), 55 (8), 43 (26) [Calc. for $C_{19}H_{29}F$ (M): 276.2253. Found: M^+ , 276.2251].

(*E*)-2-Fluoro-1-(1-naphthyl)dodec-1-ene (3c).

$\delta_H(\text{CDCl}_3)$ 0.87 (3H, t, J 7.0 Hz, 12-H), 1.15–1.30 (14H, m), 1.53–1.60 (2H, m, 4-H), 2.31 (2H, dt, $^3J_{H-F}$ 22.7, J 7.6 Hz, 3-H), 6.57 [1H, d, $^3J_{H-F(\text{olefin})}$ 20.5 Hz, 1-H], 7.30–7.53 (4H, m), 7.42–8.00 (3H, m); $\delta_F(\text{CDCl}_3)$ -103.32 (1F, m); $\delta_C(\text{CDCl}_3)$ 14.12, 22.67, 26.31, 28.74 (d, $^2J_{C-F}$ 26.4 Hz, 3-C), 28.97, 29.22, 29.28, 29.46, 29.52, 31.88, 105.56 (d, $^2J_{C-F}$ 27.3 Hz, 1-C), 124.92, 125.37, 125.93, 126.03, 126.67, 127.56, 128.34, 131.54 (d, $^3J_{C-F}$ 13.2 Hz, *ipso*-naphthyl), 132.29, 133.52, 163.29 (d, $^1J_{C-F}$ 254.4 Hz, 2-C); $\nu(\text{neat})/\text{cm}^{-1}$ 3062, 3046, 2955, 2925, 2854, 1683, 1596, 1515, 1466, 1174, 1143, 1095, 892, 842, 798, 780, 651, 626; m/z 312 (M^+ , 100%), 185 (42), 165 (17), 141 (10), 43 (3) [Calc. for $C_{22}H_{29}F$ (M): 312.2253. Found: M^+ , 312.2240] (Calc. for $C_{22}H_{29}F$: C, 84.57; H, 9.35. Found: C, 84.84; H, 9.58%).

Methyl (*E*)-10-fluoro-11-phenylundecenoate (3d).

$\delta_H(\text{CDCl}_3)$ 1.27–1.36 (8H, br s), 1.57–1.65 (4H, m), 2.29 (2H, t, J 7.6 Hz, 2-H), 2.43 (2H, dt, $^3J_{H-F}$ 23.4, J 7.6 Hz, 9-H), 3.66 (3H, s, OMe), 6.18 [1H, d, $^3J_{H-F(\text{olefin})}$ 21.9 Hz, 11-H], 7.17–7.34 (5H, m, Ph); $\delta_F(\text{CDCl}_3)$ -99.09 (1F, m); $\delta_C(\text{CDCl}_3)$ 24.91, 26.32, 28.91 (d, $^2J_{C-F}$ 24.8 Hz, 9-C), 29.07, 29.09 (3C), 34.08, 51.44, 108.09 (d, $^2J_{C-F}$ 28.9 Hz, 11-C), 126.56 (2C), 128.42 (3C), 134.34 (d, $^3J_{C-F}$ 14.1 Hz, *ipso*-Ph), 162.67 (d, $^1J_{C-F}$ 251.9 Hz, 10-C), 174.28; $\nu(\text{neat})/\text{cm}^{-1}$ 3085, 3058, 3026, 2930, 2856, 1739, 1682, 1601, 1495, 1436, 1363, 1196, 1171, 1119, 1075, 1029, 915, 885, 749, 698; m/z 292 (M^+ , 8%), 261 (5), 149 (6), 135 (17), 130 (100), 115 (12), 91 (7), 55 (6), 41 (3) [Calc. for $C_{18}H_{25}FO_2$ (M): 292.1838. Found: M^+ , 292.1838].

(E)-12-Fluoro-2,2-dimethyl-13-phenyltridec-12-en-3-one (3e).

$\delta_{\text{H}}(\text{CDCl}_3)$ 1.13 (9H, s, ^tBu), 1.25–1.36 (8H, m), 1.49–1.64 (4H, m), 2.38–2.48 (4H, m), 6.18 [1H, d, $^3J_{\text{H-F(olefin)}}$ 21.9 Hz, 13-H], 7.17–7.34 (5H, m, Ph); $\delta_{\text{F}}(\text{CDCl}_3)$ -99.06 (1F, m); $\delta_{\text{C}}(\text{CDCl}_3)$ 23.90, 26.35, 26.42 (3C), 28.95 (d, $^2J_{\text{C-F}}$ 28.2 Hz, 11-C), 29.09, 29.18, 29.26, 29.36, 36.41, 44.10, 108.07 (d, $^2J_{\text{C-F}}$ 28.0 Hz, 13-C), 126.55 (2C), 128.42 (3C), 134.39 (d, $^3J_{\text{C-F}}$ 14.1 Hz, *ipso*-Ph), 162.70 (d, $^1J_{\text{C-F}}$ 251.9 Hz, 12-C), 216.11; $\nu(\text{neat})/\text{cm}^{-1}$ 3088, 3059, 3027, 2971, 2930, 2856, 1706, 1684, 1601, 1477, 1465, 1393, 1365, 1223, 1148, 1124, 1070, 987, 914, 885, 842, 749, 698; m/z 318 (M^+ , 26%), 261 (23), 223 (7), 157 (12), 135 (30), 130 (100), 117 (23), 109 (8), 91 (52), 57 (58), 41 (17) [Calc. for $\text{C}_{21}\text{H}_{31}\text{FO}$ (M): 318.2359. Found: M^+ , 318.2347] (Calc. for $\text{C}_{21}\text{H}_{31}\text{FO}$: C, 79.20; H, 9.81. Found: C, 79.36, H, 9.96%).

(E)-11-Acetoxy-2-fluoro-1-phenylundec-1-ene (3f).

$\delta_{\text{H}}(\text{CDCl}_3)$ 1.27–1.36 (10H, m), 1.57–1.65 (4H, m), 2.05 (3H, s, MeCO), 2.43 (2H, dt, $^3J_{\text{H-F}}$ 23.4, J 7.6 Hz, 3-H), 4.05 (2H, t, J 6.7 Hz), 6.18 [1H, d, $^3J_{\text{H-F(olefin)}}$ 21.9 Hz, 1-H], 7.17–7.34 (5H, m, Ph); $\delta_{\text{F}}(\text{CDCl}_3)$ -99.12 (1F, m); $\delta_{\text{C}}(\text{CDCl}_3)$ 21.03, 25.87, 26.34, 28.59, 28.94 (d, $^2J_{\text{C-F}}$ 28.1 Hz, 3-C), 29.08, 29.21 (2C), 29.35, 64.63, 108.09 (d, $^2J_{\text{C-F}}$ 28.9 Hz, 1-C), 126.57 (2C), 128.42 (3C), 134.40 (d, $^3J_{\text{C-F}}$ 14.1 Hz, *ipso*-Ph), 162.69 (d, $^1J_{\text{C-F}}$ 252.7 Hz, 2-C), 171.26; $\nu(\text{neat})/\text{cm}^{-1}$ 3085, 3059, 3027, 2930, 2856, 1739, 1683, 1601, 1496, 1447, 1365, 1241, 1135, 1037, 915, 883, 749, 699; m/z 306 (M^+ , 12%), 246 (6), 148 (51), 130 (100), 122 (8), 115 (17), 91 (9), 69 (6), 55 (7), 43 (18) [Calc. for $\text{C}_{19}\text{H}_{27}\text{FO}_2$ (M): 306.1995. Found: M^+ , 306.1984] (Calc. for $\text{C}_{19}\text{H}_{27}\text{FO}_2$: C, 74.48; H, 8.88. Found: C, 74.59, H, 8.84%).

(E)-10-Fluoro-11-(2-methylphenyl)undec-10-en-1-ol (3g).

$\delta_{\text{H}}(\text{CDCl}_3)$ 1.20–1.40 (11H, m), 1.51–1.58 (4H, m), 2.25–2.34 (5H, m), 3.62 (2H, t, J 6.6 Hz, 1-H), 6.14 [1H, d, $^3J_{\text{H-F(olefin)}}$ 21.2 Hz, 11-H], 7.10–7.16 (4H, m, ArH); $\delta_{\text{F}}(\text{CDCl}_3)$ -101.45 (1F, m); $\delta_{\text{C}}(\text{CDCl}_3)$ 20.07, 25.69, 26.25, 28.54 (d, $^2J_{\text{C-F}}$ 27.3 Hz, 9-C), 28.96, 29.17, 29.35, 29.42, 32.79, 63.06, 106.65 (d, $^2J_{\text{C-F}}$

27.2 Hz, 11-C), 125.71, 127.08, 129.03, 129.78, 133.43 (d, $^3J_{C-F}$ 13.2 Hz, *ipso*-Ph), 136.85, 162.30 (d, $^1J_{C-F}$ 252.7 Hz, 10-C); $\nu(\text{neat})/\text{cm}^{-1}$ 3346br, 3061, 3020, 2928, 2855, 1683, 1603, 1484, 1459, 1232, 1194, 1153, 1084, 1056, 883, 846, 788, 747, 724; m/z 278 (M^+ , 43%), 260 (17), 161 (28), 149 (100), 144 (84), 136 (21), 129 (78), 118 (19), 105 (36), 93 (7), 81 (8), 69 (14), 55 (21), 41 (9) [Calc. for $C_{18}H_{27}FO$ (M): 278.2046. Found: M^+ , 278.2046].

General procedure for (*E,E*)-fluoroalkadienes (**5**)

To a mixture of benzene (5 mL) and 0.5 mL of 2 M aq. KOH (1.0 mmol), were added $Pd(OAc)_2$ (5.6 mg, 0.025 mmol) and (*S*)-(-)-BINAP (31.2 mg, 0.05 mmol). After the complete replacement of atmosphere in the flask with N_2 , an (*E*)-2-fluoro-1-iodoalk-1-ene (**2**) (0.5 mmol) and alkenylborane (1.0 mmol) were added. Then the reaction mixture was stirred under reflux for 2 h and then cooled to room temperature. The resulting solution was poured into saturated aq. NH_4Cl (20 mL) and extracted with diethyl ether (10 mL \times 3). The combined organic phase was washed with water (30 mL) and dried over $MgSO_4$. After the $MgSO_4$ was removed by filtration, the solvent was removed by evaporation. The desired product **5** was isolated in 12% yield by column chromatography (silica gel; hexane–diethyl ether).

(*5E,7E*)-8-Fluorooctadeca-5,7-diene (**5a**).

$\delta_H(\text{CDCl}_3)$ 0.86–0.92 (6H, m), 1.25–1.37 (18H, m), 1.49–1.56 (2H, m, 10-H), 2.05–2.10 (2H, m, 4-H), 2.31 (2H, dt, $^3J_{H-F}$ 23.4, J 7.3 Hz, 9-H), 5.57 (1H, dt, J 7.1, 14.9 Hz, 5-H), 5.69 [1H, dd, $^3J_{H-F(\text{olefin})}$ 20.3, J 11.0 Hz, 7-H], 5.87–5.94 (1H, m, 6-H); $\delta_F(\text{CDCl}_3)$ -104.73 (1F, m); $\delta_C(\text{CDCl}_3)$ 13.94, 14.13, 22.25, 22.71, 26.39, 28.42 (d, $^2J_{C-F}$ 27.2 Hz, 9-C), 28.97, 29.35 (2C), 29.56, 29.62, 31.59, 31.93, 32.70, 108.01 (d, $^2J_{C-F}$ 26.4 Hz, 7-C), 122.84 (d, $^3J_{C-F}$ 10.7 Hz, 6-C), 133.31 (d, $^4J_{C-F}$ 9.9 Hz, 5-C), 161.47 (d, $^1J_{C-F}$ 251.1 Hz, 8-C); $\nu(\text{neat})/\text{cm}^{-1}$ 3033, 2957, 2926, 2855, 1681, 1632, 1466, 1434, 1377, 1272, 1141, 1094, 960, 867, 722; m/z 268 (M^+ , 100%), 225 (22), 135 (12), 127 (20),

107 (15), 95 (29), 82 (97), 67 (42), 55 (29), 43 (35) [Calc. for C₁₈H₃₃F (*M*): 268.2566. Found: M⁺, 268.2564].

(3*E*,5*E*)-6-Fluorohexadeca-3,5-diene (5b).

When diisopropyl (*E*)-but-1-enylboronate was used as alkenylborane, the coupling reaction was carried out in 1,4-dioxane instead of benzene at 70 °C for 2 h.

$\delta_{\text{H}}(\text{CDCl}_3)$ 0.88 (3H, t, *J* 6.8 Hz, 16-H), 1.01 (3H, t, *J* 7.5 Hz, 1-H), 1.23–1.36 (14H, br s), 1.48–1.56 (2H, m, 8-H), 2.06–2.13 (2H, m, 2-H), 2.32 (2H, dt, ³*J*_{H-F} 23.7, *J* 7.3 Hz, 7-H), 5.58–5.73 (2H, m), 5.87–5.97 (1H, m, 4-H); $\delta_{\text{F}}(\text{CDCl}_3)$ -104.70 (1F, m); $\delta_{\text{C}}(\text{CDCl}_3)$ 13.69, 14.13, 22.70, 26.01, 26.38, 28.41 (d, ²*J*_{C-F} 27.2 Hz, 7-C), 28.97, 29.34, 29.36, 29.55, 29.61, 31.91, 107.96 (d, ²*J*_{C-F} 26.4 Hz, 5-C), 121.95 (d, ³*J*_{C-F} 10.7 Hz, 4-C), 134.77 (d, ⁴*J*_{C-F} 9.1 Hz, 3-C), 161.51 (d, ¹*J*_{C-F} 251.9 Hz, 6-C); $\nu(\text{neat})/\text{cm}^{-1}$ 3033, 2960, 2926, 2854, 1681, 1631, 1463, 1376, 1319, 1242, 1173, 1141, 1092, 1013, 959, 867, 775, 721; *m/z* 240 (M⁺, 100%), 149 (6), 135 (11), 127 (8), 121 (13), 113 (40), 107 (14), 99 (77), 85 (42), 81 (33), 67 (38), 59 (12), 55 (38), 43 (57) [Calc. for C₁₆H₂₉F (*M*): 240.2253. Found: M⁺, 240.2253].

Ethyl (4*E*,6*E*)-7-fluoro-2,2-dimethylheptadeca-4,6-dienoate (5c).

$\delta_{\text{H}}(\text{CDCl}_3)$ 0.88 (3H, t, *J* 7.1 Hz, 17-H), 1.16 (6H, s, Me × 2), 1.22–1.34 (17H, m), 1.48–1.53 (2H, m, 9-H), 2.26–2.35 (4H, m), 4.11 (2H, q, *J* 7.1 Hz, OCH₂CH₃), 5.46–5.53 (1H, m, 4-H), 5.69 [1H, dd, ³*J*_{H-F(olefin)} 20.2, *J* 11.0 Hz, 6-H], 5.90–5.97 (1H, m, 5-H); $\delta_{\text{F}}(\text{CDCl}_3)$ -99.92 (1F, m); $\delta_{\text{C}}(\text{CDCl}_3)$ 14.13, 14.28, 22.69, 24.85 (2C), 26.38, 28.45 (d, ²*J*_{C-F} 27.2 Hz, 8-C), 28.96, 29.33, 29.35, 29.54, 29.59, 31.91, 42.59, 43.90, 60.32, 107.83 (d, ²*J*_{C-F} 27.3 Hz, 6-C), 126.12 (d, ³*J*_{C-F} 11.5 Hz, 5-C), 128.02 (d, ⁴*J*_{C-F} 9.9 Hz, 4-C), 162.17 (d, ¹*J*_{C-F} 253.6 Hz, 7-C), 177.42; $\nu(\text{neat})/\text{cm}^{-1}$ 3032, 2957, 2927, 2855, 1731, 1679, 1631, 1469, 1386, 1365, 1303, 1242, 1196, 1147, 1095, 1029, 964, 865, 768, 722; *m/z* 340 (M⁺, 23%), 266 (18), 225 (100), 205 (6), 149 (5), 135 (12), 121 (21), 107 (14), 93 (23), 79 (22), 67 (32), 55 (22), 43 (27) [Calc. for C₂₁H₃₇FO₂

(*M*): 340.2777. Found: M⁺, 340.2791] (Calc. for C₂₁H₃₇FO₂: C, 74.07; H, 10.95. Found: C, 74.03; H, 10.98%).

Methyl (10*E*,12*E*)-10-fluoroheptadeca-10,12-dienoate (5d).

$\delta_{\text{H}}(\text{CDCl}_3)$ 0.90 (3H, t, *J* 7.1 Hz, 17-H), 1.27–1.38 (12H, m), 1.48–1.65 (4H, m), 2.05–2.10 (2H, m, 14-H), 2.26–2.36 (4H, m), 3.67 (3H, s, OMe), 5.54–5.61 (1H, m, 13-H), 5.69 [1H, dd, $^3J_{\text{H-F(olefin)}}$ 20.5, *J* 11.0 Hz, 11-H], 5.86–5.93 (1H, m, 12-H); $\delta_{\text{F}}(\text{CDCl}_3)$ -104.53 (1F, m); $\delta_{\text{C}}(\text{CDCl}_3)$ 13.94, 22.24, 24.94, 26.35, 28.40 (d, $^2J_{\text{C-F}}$ 27.3 Hz, 9-C), 28.87, 29.11, 29.13 (2C), 31.58, 32.69, 34.09, 51.44, 108.04 (d, $^2J_{\text{C-F}}$ 27.2 Hz, 11-C), 122.79 (d, $^3J_{\text{C-F}}$ 10.7 Hz, 12-C), 133.38 (d, $^4J_{\text{C-F}}$ 9.8 Hz, 13-C), 161.36 (d, $^1J_{\text{C-F}}$ 251.9 Hz, 10-C), 174.29; $\nu(\text{neat})/\text{cm}^{-1}$ 3029, 2955, 2929, 2857, 1741, 1680, 1631, 1459, 1436, 1364, 1197, 1171, 1119, 1077, 1027, 962, 868, 721; *m/z* 298 (M⁺, 76%), 278 (11), 267 (23), 238 (6), 224 (5), 208 (12), 177 (8), 161 (20), 149 (17), 136 (88), 127 (11), 121 (38), 107 (48), 93 (78), 85 (72), 79 (94), 67 (75), 59 (38), 55 (100), 41 (80) [Calc. for C₁₈H₃₁FO₂ (*M*): 298.2308. Found: M⁺, 298.2308] (Calc. for C₁₈H₃₁FO₂: C, 72.44; H, 10.47. Found: C, 72.35; H, 10.36%).

(10*E*,12*E*)-10-Fluoropentadeca-10,12-dien-1-ol (5e).

When diisopropyl (*E*)-but-1-enylboronate was used as alkenylborane, the coupling reaction was carried out in 1,4-dioxane instead of benzene at 70 °C for 2 h.

$\delta_{\text{H}}(\text{CDCl}_3)$ 1.01 (3H, t, *J* 7.6 Hz, 15-H), 1.22–1.38 (11H, m), 1.51–1.58 (4H, m), 2.06–2.13 (2H, m, 14-H), 2.32 (2H, dt, $^3J_{\text{H-F}}$ 23.4, *J* 7.3 Hz, 9-H), 3.64 (2H, t, *J* 6.6 Hz, 1-H), 5.59–5.74 (2H, m), 5.87–5.93 (1H, m, 12-H); $\delta_{\text{F}}(\text{CDCl}_3)$ -104.73 (1F, m); $\delta_{\text{C}}(\text{CDCl}_3)$ 13.70, 25.72, 26.00, 26.36, 28.39 (d, $^2J_{\text{C-F}}$ 27.2 Hz, 9-C), 28.92, 29.26, 29.38, 29.46, 32.79, 63.08, 107.99 (d, $^2J_{\text{C-F}}$ 27.3 Hz, 11-C), 121.90 (d, $^3J_{\text{C-F}}$ 10.7 Hz, 12-C), 134.82 (d, $^4J_{\text{C-F}}$ 9.9 Hz, 13-C), 161.45 (d, $^1J_{\text{C-F}}$ 252.0 Hz, 10-C); $\nu(\text{neat})/\text{cm}^{-1}$ 3313 (br), 3033, 2963, 2929, 2855, 1680, 1631, 1461, 1434, 1371, 1320, 1150, 1128, 1077, 1057, 960, 867, 722; *m/z* 242 (M⁺, 45%), 224 (5), 153 (16), 135 (14), 125 (34), 112 (62), 97

(100), 79 (71), 67 (68), 55 (94), 41 (83) [Calc. for C₁₅H₂₇FO (*M*): 242.2046. Found: M⁺, 242.2050].

(5*E*,7*E*)-17-Chloro-8-fluoroheptadeca-5,7-diene (5f).

$\delta_{\text{H}}(\text{CDCl}_3)$ 0.90 (3H, t, *J* 7.6 Hz, 1-H), 1.28–1.46 (14H, m), 1.48–1.57 (2H, m), 1.73–1.80 (2H, m, 10-H), 2.05–2.08 (2H, m, 4-H), 2.34 (2H, dt, $^3J_{\text{H-F}}$ 23.4, *J* 7.3 Hz, 9-H), 3.52 (2H, t, *J* 6.6 Hz, 17-H), 5.54–5.61 (1H, m, 5-H), 5.69 [1H, dd, $^3J_{\text{H-F(olefin)}}$ 20.2, *J* 11.0 Hz, 7-H], 5.87–5.93 (1H, m, 6-H); $\delta_{\text{F}}(\text{CDCl}_3)$ -104.85 (1F, m); $\delta_{\text{C}}(\text{CDCl}_3)$ 13.95, 22.23, 26.34, 26.87, 28.39 (d, $^2J_{\text{C-F}}$ 27.2 Hz, 9-C), 28.85, 28.88, 29.23, 29.33, 31.58, 32.64, 32.69, 45.17, 108.04 (d, $^2J_{\text{C-F}}$ 27.2 Hz, 7-C), 122.78 (d, $^3J_{\text{C-F}}$ 10.7 Hz, 6-C), 133.38 (d, $^4J_{\text{C-F}}$ 9.0 Hz, 5-C), 161.36 (d, $^1J_{\text{C-F}}$ 251.9 Hz, 8-C); $\nu(\text{neat})/\text{cm}^{-1}$ 3029, 2959, 2928, 2856, 1680, 1631, 1465, 1375, 1147, 1075, 962, 868, 726, 653; *m/z* 288 (M⁺, 50%), 245 (17), 232 (5), 135 (6), 127 (22), 121 (16), 107 (16), 95 (27), 82 (100), 67 (53), 55 (48), 41 (51) [Calc. for C₁₇H₃₀ClF (*M*): 288.2020. Found: M⁺, 288.2027] (Calc. for C₁₇H₃₀ClF: C, 70.68; H, 10.47. Found: C, 70.48; H, 10.25%).

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Chapter 5

Stereoselective Synthesis of Fluorinated Analogs of Insect Sex Pheromones by Pd-Catalyzed Cross-Coupling Reaction of Fluoroiodoalkenes with Alkenylboranes

Abstract

Fluorinated analogs of insect sex pheromones, (*9E,11E*)-9-fluorotetradeca-9,11-dienyl acetate and (*10E,12E*)-13-fluorohexadeca-10,12-dien-1-ol were stereoselectively synthesized by Pd-catalyzed cross-coupling reaction using (*E*)-2-fluoro-1-iodoalk-1-enes with organoboranes.

Introduction

Fluorinated analogs of insect sex pheromones have been of great interest because substitution of a fluorine atom for a hydrogen can be expected to exert influence on their activities by increasing their stability, hydrophobicity or polarity without steric consequences.¹ They are also expected to act as antipheromones by interfering with the perception process of the natural pheromone.² Although many fluorinated analogs of insect pheromones have been synthesized, the fluorine atoms are mostly introduced at the saturated carbon, and only a few analogs having a fluorine on their double bond have been synthesized.³ In Chapter 4, a variety of fluoroalkenes and fluoroalkadienes were stereoselectively synthesized by Pd-catalyzed cross-coupling reactions of (*E*)-2-fluoro-1-iodoalk-1-enes with organoboranes.^{6,7} In order to show the usefulness of this method, stereoselective synthesis of biologically active compounds having an fluoroalkene moiety was attempted. As an appropriate bioactive compound, the author chose (9*Z*,11*E*)-tetradeca-9,11-dienyl acetate (**1**),⁴ which is a sex pheromone of the Egyptian cotton leaf worm "*Spodoptera-Littorails-Boisd*". Synthesis of a fluorinated analog of a sex pheromone of the silkworm moth "*Bombyx mori*", (10*E*,12*Z*)-hexadeca-10,12-dien-1-ol (**2**) (bombykol),⁵ was also planned (Figure 1).

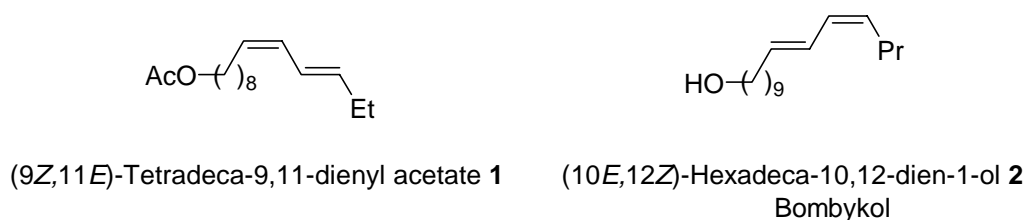


Figure 1. Sex pheromones of *Spodoptera-Littorails-Boisd* and *Bombyx mori*.

The compounds **1** and **2** have an (*E,Z*)-diene structure in their molecules, and an 11-fluoro analog of **1** and a 12-fluoro analog of **2** were previously synthesized by Camps *et al.* using the Wittig reaction with

α -fluoro- α,β -unsaturated aldehydes (Figure 2).^{3b} However, the stereoselective introduction of a fluorine atom at C-9 of **1** and C-13 of **2** had not been achieved. The author planned to synthesize a 9-fluoro analog of **1**, (9*E*,11*E*)-9-fluorotetradeca-9,11-dienyl acetate (**3**), from (*E*)-9-fluoro-10-iododec-9-en-1-ol (**5a**) and a 13-fluoro analog of **2**, (10*E*,12*E*)-13-fluorohexadeca-10,12-dien-1-ol (**4**), from (*E*)-2-fluoro-1-iodopent-1-ene (**5c**) by Pd-catalyzed cross-coupling reaction with alkenylboranes (Scheme 1).

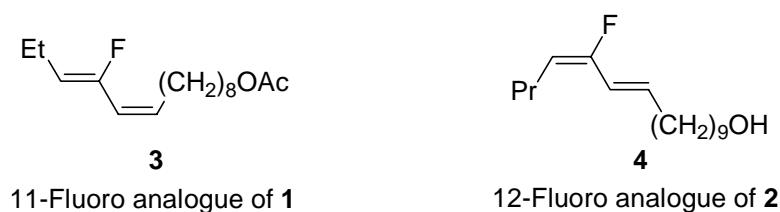
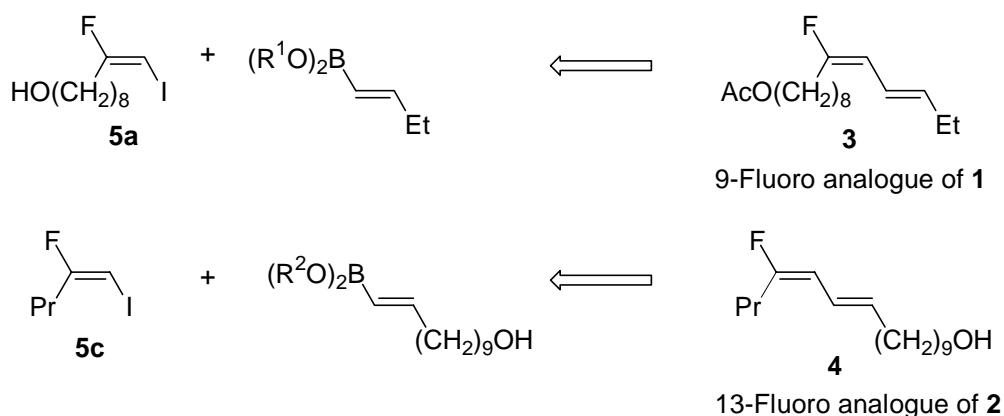


Figure 2.



Scheme 1.

Results and discussion

Synthesis of (9*E*,11*E*)-9-fluorotetradeca-9,11-dienyl acetate (**3**)

The cross-coupling reaction of (*E*)-9-fluoro-10-iododec-9-en-1-ol (**5a**)⁸ with diisopropyl (*E*)-but-1-enylboronate was carried out in the presence of Pd(OAc)₂, 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP), and KOH in dioxane under reflux conditions (refer to Chapter 4).⁷ The reaction smoothly proceeded and (9*E*,11*E*)-9-fluorotetradeca-9,11-dien-1-ol (**6**) was stereoselectively obtained in 67% yield. In the ¹H-NMR spectrum of **6**, the coupling constant between 11-H and 12-H was 15.1 Hz which showed that the double bond had *trans*-configuration (Figure 3). The coupling constant between fluorine and 10-H was 20.2 Hz which showed that the other double bond had *cis*-configuration.

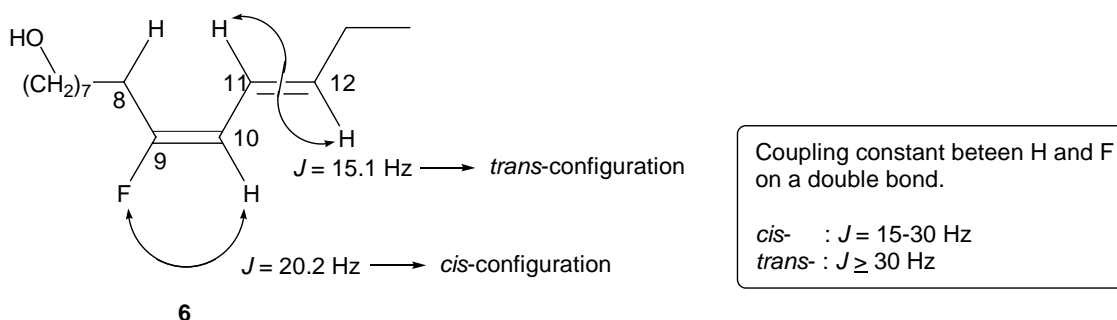
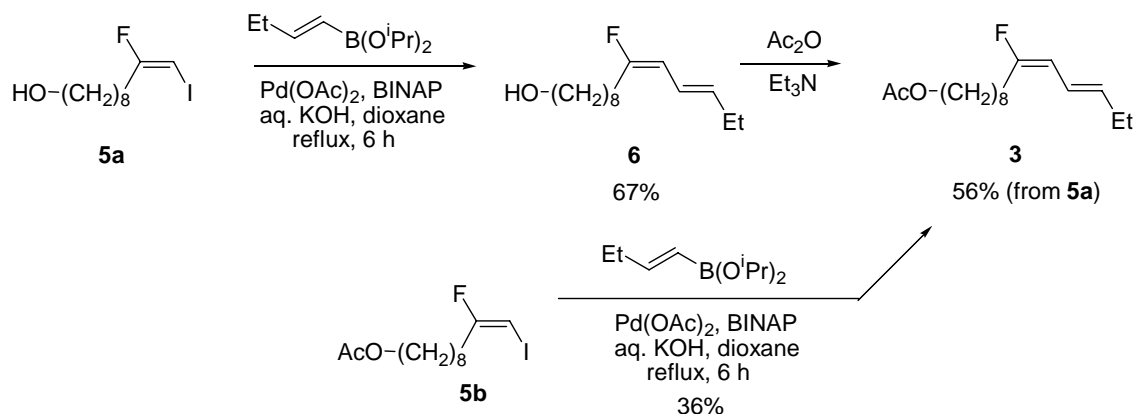


Figure 3.

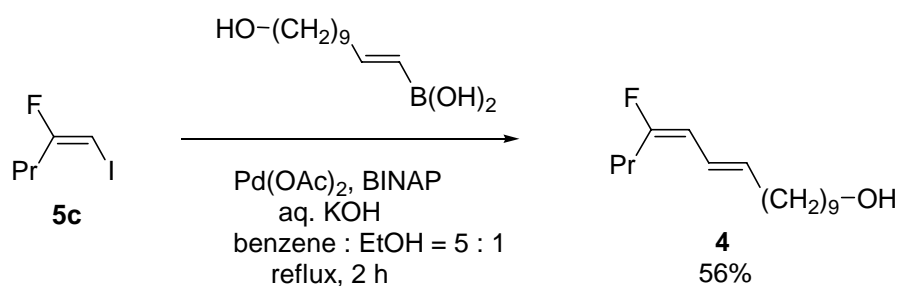
Consequently, the (*E,E*)-diene structure in **6** could be formed. After acetylation of **6** with acetic anhydride, the desired product, (9*E*,11*E*)-9-fluorotetradeca-9,11-dienyl acetate (**3**), was obtained in 56% overall yield from **5a** (Scheme 2). The cross-coupling reaction of (*E*)-9-fluoro-10-iododec-1-enyl acetate (**5b**) with diisopropyl (*E*)-but-1-enylboronate could provide **3** in one step; however, the coupling reaction was sluggish and **3** was obtained only in 36% yield.



Scheme 2. Synthesis of (9*E*,11*E*)-9-fluorotetradeca-9,11-dienyl acetate.

Synthesis of (10*E*,12*E*)-13-fluorohexadeca-10,12-dien-1-ol (a fluorinated analog of bombykol) (4)

A fluorinated analog of bombykol, (10*E*,12*E*)-13-fluorohexadeca-10,12-dien-1-ol (4), was synthesized by the coupling reaction of (*E*)-2-fluoro-1-iodopent-1-ene (5c)⁸ with (*E*)-11-hydroxyundec-1-enylboronic acid. The reaction was completed in 2 h, and 4 was stereoselectively obtained in 56% yield (Scheme 3). The (*E,E*)-stereochemistry of the double bonds in 4 was determined from the coupling constant between F and 12-H ($J = 20.5$ Hz) and that between 10-H and 11-H ($J = 14.9$ Hz).¹⁰



Scheme 3. Synthesis of (10*E*,12*E*)-13-fluorohexadeca-10,12-dien-1-ol.

Conclusion

Pd-catalyzed cross-coupling reaction of (*E*)-2-fluoro-1-iodoalk-1-ene with alkenylboronates could be applied to the stereoselective synthesis of fluorinated analogs of insect sex pheromones, (*9E,11E*)-9-fluorotetradeca-9,11-dienyl acetate (**3**) and (*10E,12E*)-13-fluorohexadeca-10,12-dien-1-ol (**4**).

Experimental

General.

The IR spectra were recorded using a JASCO FT/IR-410. The ^1H -NMR (400 MHz), ^{19}F -NMR (376 MHz) and ^{13}C -NMR (100 MHz) spectra were recorded in CDCl_3 on a JEOL JNM-A400II FT NMR and the chemical shifts, δ , are referred to TMS (^1H , ^{13}C) and CFCl_3 (^{19}F). The low- and high-resolution mass spectra were measured on a JEOL JMS-700TZ, JMS-FABmate or JMS-HX110. For column chromatography, Merck silica gel 7734 was used, and for analytical thin layer chromatography, Merck silica gel 5715 was used. BINAP was purchased from Kanto Kagaku Co., Ltd. and was used as supplied. Diisopropyl (*E*)-but-1-enylboronate^{11a} and (*E*)-11-hydroxyundec-1-enylboronic acid^{11b,c} were prepared according to the literatures. $\text{Pd}(\text{OAc})_2$ was purchased from Tokyo Kasei Co., Ltd. and was used as supplied. The procedures for the preparation of (*E*)-2-fluoro-1-iodoalk-1-enes (**5a-c**) have been shown in Chapter 1.

(9*E*,11*E*)-9-Fluorotetradeca-9,11-dien-1-ol (**6**).

To a mixture of dioxane (3 mL) and 0.5 mL of 2 M aq. KOH (1.0 mmol) were added $\text{Pd}(\text{OAc})_2$ (5.6 mg, 0.025 mmol) and (S)-(-)-BINAP (15.6 mg, 0.025 mmol). After the complete replacement of atmosphere in the flask with N_2 , **5a** (150 mg, 0.5 mmol) and diisopropyl (*E*)-but-1-enyl boronate (244 mg, 1.0 mmol) were added. Then the reaction mixture was stirred at 70 °C for 6 h and then cooled to room temperature. The resulting mixture was poured into saturated aq. NaHCO_3 (20 mL) and extracted with diethyl ether (10 mL \times 3). The combined organic phase was dried over MgSO_4 and concentrated under reduced pressure. The product **6** was isolated by column chromatography (silicagel; hexane-diethyl ether).

Oil; $\delta_{\text{H}}(\text{CDCl}_3)$ 1.01 (3H, t, J 7.6 Hz, 14- H_3), 1.25-1.41 (9H, m), 1.52-1.63 (4H, m), 2.06-2.13 (2H, m, 13- H_2), 2.32 (2H, dt, $^3J_{\text{H-F}}$ 23.4, J 7.3 Hz, 8- H_2),

3.64 (2H, t, J 6.6 Hz, 1-H₂), 5.59-5.74 (2H, m), 5.87-5.94 (1H, m, 11-H); $\delta_{\text{F}}(\text{CDCl}_3)$ -104.75 (1F, m); $\delta_{\text{C}}(\text{CDCl}_3)$ 13.69, 25.70, 25.99, 26.34, 28.38 (d, $^2J_{\text{C-F}}$ 27.2 Hz, 8-C), 28.85, 29.28, 29.70, 32.77, 63.07, 108.00 (d, $^2J_{\text{C-F}}$ 27.2 Hz, 10-C), 121.89 (d, $^3J_{\text{C-F}}$ 11.6 Hz, 11-C), 134.84 (d, $^4J_{\text{C-F}}$ 9.9 Hz, 12-C), 161.45 (d, $^1J_{\text{C-F}}$ 252.0 Hz, 9-C); $\nu(\text{neat})/\text{cm}^{-1}$ 3346br, 3032, 2959, 2930, 2856, 1680, 1631, 1461, 1435, 1371, 1319, 1127, 1075, 960, 868; m/z 228 (M⁺, 26%), 210 (5), 153 (7), 139 (7), 133 (6), 125 (20), 121 (8), 111 (34), 108 (23), 97 (100), 93 (42), 85 (38), 79 (45), 73 (12), 67 (43), 59 (16), 55 (72), 47 (6), 41 (56) [Calc. for C₁₄H₂₅FO (M): 228.1889. Found: M⁺, 228.1897].

(9*E*,11*E*)-9-Fluorotetradeca-9,11-dienyl acetate (3).

To a stirred solution of **6** (114 mg, 0.5 mmol) in CH₂Cl₂ (3 mL) was added acetic anhydride (61 mg, 1.2 mmol) and Et₃N (61 mg, 1.2 mmol) at room temperature. After stirring for 12 h, the reaction mixture was poured into water (20 mL) and extracted with diethyl ether (10 mL \times 3). The combined organic phase was dried over MgSO₄ and concentrated under reduced pressure. The product **3** was isolated by column chromatography (silicagel; hexane-diethyl ether).

Oil; $\delta_{\text{H}}(\text{CDCl}_3)$ 1.01 (3H, t, J 7.6 Hz, 14-H₃), 1.26-1.42 (8H, brs), 1.50-1.65 (4H, m), 2.05 (3H, s, MeCO), 2.06-2.14 (2H, m, 13-H₂), 2.32 (2H, dt, $^3J_{\text{H-F}}$ 23.4, J 7.3 Hz, 8-H₂), 4.05 (2H, t, J 6.6 Hz, 1-H₂), 5.59-5.74 (2H, m), 5.87-5.94 (1H, m, 11-H); $\delta_{\text{F}}(\text{CDCl}_3)$ -104.79 (1F, m); $\delta_{\text{C}}(\text{CDCl}_3)$ 13.69, 21.02, 25.87, 25.99, 26.32, 28.36 (d, $^2J_{\text{C-F}}$ 27.3 Hz, 8-C), 28.58, 28.83, 29.12, 29.20, 64.60, 108.03 (d, $^2J_{\text{C-F}}$ 27.3 Hz, 10-C), 121.88 (d, $^3J_{\text{C-F}}$ 11.5 Hz, 11-C), 134.85 (d, $^4J_{\text{C-F}}$ 9.0 Hz, 12-C), 161.37 (d, $^1J_{\text{C-F}}$ 252.0 Hz, 9-C), 171.23; $\nu(\text{neat})/\text{cm}^{-1}$ 3034, 2960, 2932, 2857, 1741, 1680, 1631, 1462, 1435, 1365, 1241, 1133, 1038, 962, 868, 723; m/z 270 (M⁺, 15%), 210 (14), 167 (6), 153 (12), 147 (6), 139 (8), 126 (23), 119 (7), 112 (37), 97 (100), 85 (21), 79 (26), 67 (21), 59 (8), 55 (30), 43 (64) [Calc. for C₁₆H₂₇FO₂ (M): 270.1995. Found: M⁺, 270.1992].

(10*E*,12*E*)-13-Fluorohexadeca-10,12-dien-1-ol (4).

To a mixture of benzene (5 mL), ethanol (1 mL) and 0.5 mL of 2 M aq. KOH (1.0 mmol) were added Pd(OAc)₂ (5.6 mg, 0.025 mmol) and (S)-(-)-BINAP (31.2 mg, 0.05 mmol). After the complete replacement of atmosphere in the flask with N₂, **5c** (107 mg, 0.5 mmol) and (*E*)-(11-hydroxyundec-1-enyl)boronic acid (214 mg, 1.0 mmol) were added. The reaction mixture was stirred under reflux for 2 h and then cooled to room temperature. The resulting mixture was poured into saturated aq. NaHCO₃ (20 mL) and the separated aqueous phase was extracted with diethyl ether (10 mL × 3). The combined organic phase was dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by column chromatography to afford a mixture of **4** and undec-10-en-1-ol derived from (*E*)-(11-hydroxyundec-1-enyl)boronic acid. Undec-10-en-1-ol was removed under reduced pressure (132-133 °C / 15 mmHg).

Oil; δ_H(CDCl₃) 0.95 (3H, t, *J* 7.3 Hz, 16-H₃), 1.23-1.47 (13H, m), 1.52-1.61 (4H, m), 2.04-2.09 (2H, m, 9-H₂), 2.30 (2H, dt, ³*J*_{H-F} 23.7, *J* 7.3 Hz, 14-H₂), 3.63 (2H, t, *J* 6.6 Hz, 1-H₂), 5.58 (1H, dt, *J* 7.0, 14.9 Hz, 10-H), 5.71 [1H, dd, ³*J*_{H-F(olefin)} 20.5, *J* 11.2 Hz, 12-H], 5.87-5.94 (1H, m, 11-H); δ_F(CDCl₃) -104.91 (1F, m); δ_C(CDCl₃) 13.47, 15.28, 19.75, 25.73, 29.17, 29.42 (2C), 29.55, 30.33 (d, ²*J*_{C-F} 27.2 Hz, 14-C), 32.80, 32.99, 63.07, 108.24 (d, ²*J*_{C-F} 26.5 Hz, 12-C), 122.82 (d, ³*J*_{C-F} 10.8 Hz, 11-C), 133.37 (d, ⁴*J*_{C-F} 9.9 Hz, 10-C), 161.21 (d, ¹*J*_{C-F} 251.4 Hz, 13-C); ν(neat)/cm⁻¹ 3345br, 3031, 2962, 2927, 2854, 1679, 1631, 1464, 1434, 1369, 1145, 1067, 961, 868, 839; m/z 256 (M⁺, 24%), 236 (7), 153 (7), 140 (7), 135 (8), 127 (36), 121 (14), 114 (83), 107 (35), 99 (76), 91 (23), 85 (100), 79 (37), 67 (31), 59 (15), 55 (31), 41 (28) [Calc. for C₁₆H₂₉FO (M): 256.2202. Found: M⁺, 256.2196].

(*E*)-9-Fluoro-10-iododec-9-en-1-ol (5a).

Oil; δ_H(CDCl₃) 1.25-1.42 (9H, m), 1.50-1.63 (4H, m), 2.50 (2H, dt, ³*J*_{H-F} 22.7, *J* 7.6 Hz, 8-H₂), 3.65 (2H, t, *J* 6.8 Hz, 1-H₂), 5.67 [1H, d, ³*J*_{H-F(olefin)} 17.8 Hz,

10-H]; $\delta_{\text{F}}(\text{CDCl}_3)$ -82.51 [1F, dt, ${}^3J_{\text{H-F}}$ 22.7, ${}^3J_{\text{H-F(olefin)}}$ 17.8 Hz]; $\delta_{\text{C}}(\text{CDCl}_3)$ 25.69 (2C), 28.64, 29.22, 29.24, 30.91 (d, ${}^2J_{\text{C-F}}$ 26.4 Hz, 8-C), 32.74, 54.75 (d, ${}^2J_{\text{C-F}}$ 40.5 Hz, 10-C), 63.02, 164.14 (d, ${}^1J_{\text{C-F}}$ 264.4 Hz, 9-C); $\nu(\text{neat})/\text{cm}^{-1}$ 3335br, 3076, 2929, 2856, 1650, 1464, 1430, 1118, 1073, 871, 771, 713; m/z 300 (M^+ , 2%), 198 (63), 185 (6), 173 (12), 153 (52), 135 (100), 128 (3), 109 (47), 93 (48), 79 (28), 71 (42), 55 (32), 41 (11) [Calc. for $\text{C}_{10}\text{H}_{18}\text{FIO}$ (M): 300.0386. Found: M^+ , 300.0370].

(*E*)-9-Fluoro-10-iododec-9-enyl acetate (5b).

Oil; $\delta_{\text{H}}(\text{CDCl}_3)$ 1.29-1.39 (8H, m), 1.52-1.66 (4H, m), 2.05 (3H, s, Me), 2.50 (2H, dt, ${}^3J_{\text{H-F}}$ 22.7, J 7.3 Hz, 3- H_2), 4.06 (2H, t, J 6.6 Hz, 10- H_2), 5.67 [1H, d, ${}^3J_{\text{H-F(olefin)}}$ 17.8 Hz, 1-H]; $\delta_{\text{F}}(\text{CDCl}_3)$ -82.55 [1F, dt, ${}^3J_{\text{H-F}}$ 22.7, ${}^3J_{\text{H-F(olefin)}}$ 17.8 Hz]; $\delta_{\text{C}}(\text{CDCl}_3)$ 21.03, 25.67, 25.85, 28.57, 28.61, 29.06, 29.12, 30.91 (d, ${}^2J_{\text{C-F}}$ 25.6 Hz, 3-C), 54.76 (d, ${}^2J_{\text{C-F}}$ 40.5 Hz, 1-C), 64.58, 164.12 (d, ${}^1J_{\text{C-F}}$ 263.4 Hz, 2-C), 171.22; $\nu(\text{neat})/\text{cm}^{-1}$ 3076, 2931, 2857, 1740, 1650, 1465, 1431, 1388, 1365, 1240, 1124, 1077, 1038, 865, 772, 723; m/z 343 ($\text{M}^+\text{+H}$, 22%), 263 (5), 165 (3), 120 (11), 107 (21), 99 (4), 89 (18), 77 (15), 61 (5), 55 (4), 43 (11) [HR FAB-MS: Calc. for $\text{C}_{12}\text{H}_{21}\text{FIO}_2$ ($M + \text{H}$): 343.0570. Found: M^+ , 343.0559].

(*E*)-2-Fluoro-1-iodopent-1-ene (5c).

Oil; $\delta_{\text{H}}(\text{CDCl}_3)$ 0.98 (3H, t, J 7.3 Hz, 5- H_3), 1.55-1.64 (2H, m, 4- H_2), 2.49 (2H, dt, ${}^3J_{\text{H-F}}$ 22.4, J 7.3 Hz, 3- H_2), 5.69 [1H, d, ${}^3J_{\text{H-F(olefin)}}$ 17.8 Hz, 1-H]; $\delta_{\text{F}}(\text{CDCl}_3)$ -82.40 [1F, dt, ${}^3J_{\text{H-F}}$ 22.4, ${}^3J_{\text{H-F(olefin)}}$ 17.8 Hz]; $\delta_{\text{C}}(\text{CDCl}_3)$ 13.30, 19.24, 32.79 (d, ${}^2J_{\text{C-F}}$ 25.6 Hz, 3-C), 54.65 (d, ${}^2J_{\text{C-F}}$ 39.7 Hz, 1-C), 163.98 (d, ${}^1J_{\text{C-F}}$ 264.7 Hz, 2-C); $\nu(\text{neat})/\text{cm}^{-1}$ 3078, 2965, 2935, 2874, 1651, 1463, 1430, 1122, 1066, 1027, 854, 773; m/z 214 (M^+ , 9%), 185 (41), 172 (9), 149 (7), 127 (7), 83 (21), 69 (20), 59 (36), 44 (19), 39 (11) [Calc. for $\text{C}_5\text{H}_8\text{FI}$ (M): 213.9657. Found: M^+ , 213.9659].

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Chapter 6

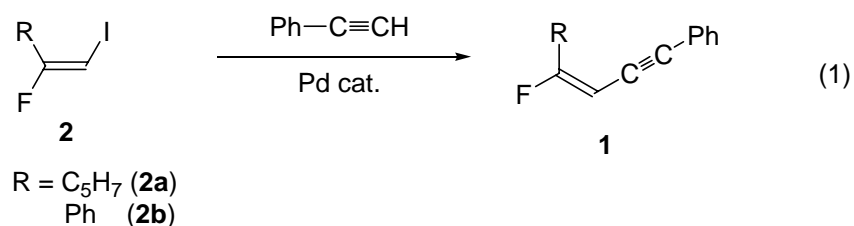
Stereoselective Synthesis of (*E*)-1-Fluoro-1,3-enynes via Pd-Catalyzed Coupling Reaction of (*E*)-2-Fluoro-1-iodoalk-1-enes with alk-1-ynes

Abstract

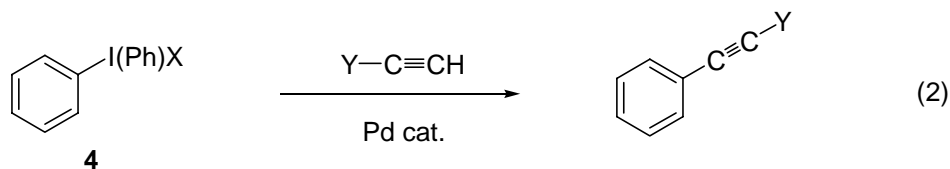
Cross-coupling reaction of (*E*)-2-fluoro-1-iodoalk-1-enes with alk-1-ynes was carried out in the presence of a Pd catalyst to synthesize (*E*)-1-fluoro-1,3-enynes stereoselectively. As the reaction proceeds under mild conditions, polyfunctionalized 1-fluoro-1,3-enynes could be prepared, and synthesis of a fluorinated analog of 11,12-dehydrocorioric acid, which has inhibitory activity against rice blast fungus, was achieved by this method.

Introduction

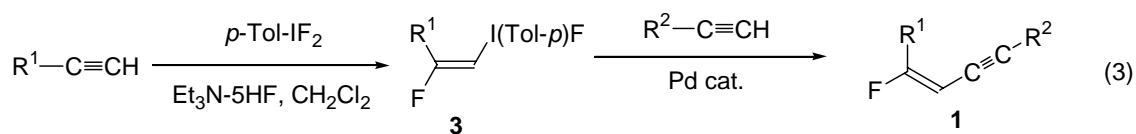
Fluorinated organic compounds have been of great interest to synthetic and medicinal chemists due to the unique physical and biological properties imparted by fluorine.¹ Significant efforts have been exerted to achieve the synthesis of fluorinated enynes for their use as building blocks in the preparation of the fluorinated organic compounds.² Although the stereoselective syntheses of difluoro-1,3-enynes^{3a-c} and 2-fluoro-1,3-enynes^{3d,e} have been reported, selective methods for the 1-fluoro-1,3-enynes had been unknown.⁴ Mestdagh *et al.* reported that (*E*)-1-fluoro-1,3-enynes (**1**) could be stereoselectively synthesized by a Pd-catalyzed cross-coupling reaction using (*E*)-2-fluoro-1-iodoalk-1-enes (**2**) with phenylacetylene in the presence of CuI and amine (Sonogashira reaction).⁵ However, they synthesized only two simple fluoroenynes, (*E*)-4-fluoro-1-phenylnon-3-en-1-yne (**1a**) and (*E*)-2-fluoro-1,4-diphenylbut-1-en-3-yne (**1b**), from the corresponding (*E*)-2-fluoro-1-iodoalk-1-enes (**2a,b**) and phenylacetylene [Eq. (1)]. Since natural organic compounds usually have various functionalities in their structure, the synthesis of polyfunctionalized fluoroenynes is required for application to the fluorinated analogs of natural compounds.⁴



Recently, Stang *et al.* reported the Sonogashira reaction using diaryliodonium salts (**4**) [Eq. (2)].⁶

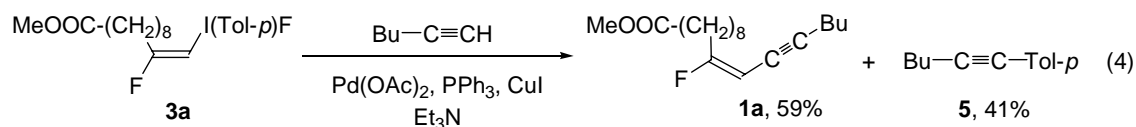


Since (*E*)-2-fluoroalk-1-enyliodonium fluorides (**3**) having various functional groups can be synthesized from alk-1-ynes as shown in Chapter 1,⁷ the author employed the fluoroalkenyliodonium salts (**3**) in the Sonogashira reaction to synthesize polyfunctionalized (*E*)-1-fluoro-1,3-dienes (**1**) [Eq. (3)].⁸

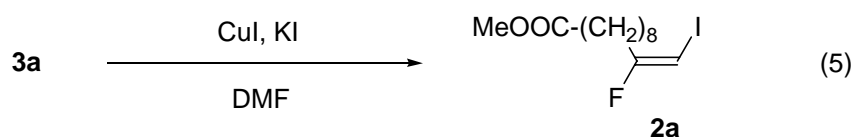


Results and Discussion

The coupling reaction of (*E*)-10-methoxycarbonyl-2-fluorodec-1-enyliodonium salt (**3a**)⁷ with hex-1-yne was carried out in the presence of Pd(OAc)₂, PPh₃, CuI and Et₃N [Eq. (4)].^{4,7}



The reaction smoothly proceeded to yield methyl (*E*)-10-fluoroheptadec-10-en-12-ynoate (**1a**) in 59%; however, a substantial amount of *p*-tolylhexyne (**5**) was also obtained (41%). As iodotoluene is formed in the reaction of **3a** with hex-1-yne and the cross-coupling reaction of iodotoluene with hex-1-yne proceeds under mild conditions,⁹ the formation of **5** is unavoidable as long as **3a** is used. Application of hex-1-ynylstannane instead of hex-1-yne gave a similar result, and the formation of **5** could not be suppressed.⁸ Consequently, the author converted **3a** to methyl (*E*)-10-fluoro-11-iodoundec-10-enoate (**2a**) (refer to Chapter 1) [Eq. (5)],⁷ and examined the cross-coupling reaction using **2a**.



The coupling reaction between **2a** and hex-1-yne was examined in the presence of a Pd catalyst, CuI and amine at room temperature (Table 1). When 8 mol% of CuI was used, a significant amount of the hex-1-yne dimer was formed (Entry 1) and 2 equiv. of hex-1-yne was necessary to obtain fluoroenyne (**1a**) in good yield (Entry 2).¹⁰ By using 16 mol% of CuI, the formation of the dimer could be suppressed, and **1a** was obtained in good yield with 1.2 equiv. of hex-1-yne (Entry 3). As for the Pd catalyst,

Pd(OAc)₂ was found to be more effective than Pd₂dba₃ (Entries 6 and 7). When the reaction was carried out using 16 mol% of CuI, 5 mol% of Pd(OAc)₂ and 2PPh₃ in Et₂NH, the best result was obtained (Entry 6).

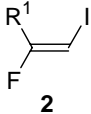
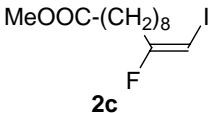
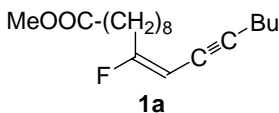
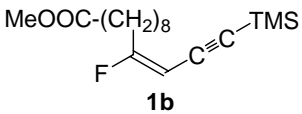
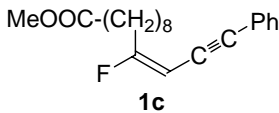
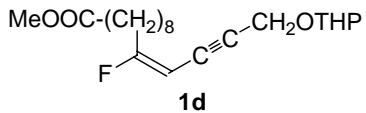
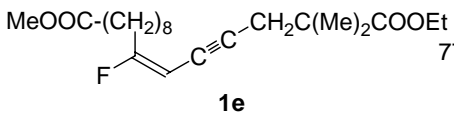
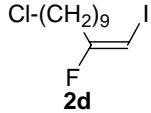
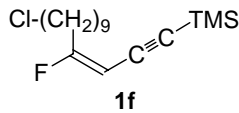
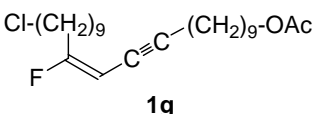
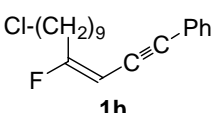
Table 1. Cross-coupling reaction of **2a** with hex-1-yne using various catalysts and amines.

Entry	Solvent	Catalyst	Amine ^a	CuI / 2a	Hexyne / 2a	Yield / % ^b
1	DMF	Pd ₂ dba ₃ + 4PPh ₃	Et ₃ N	0.08	1.2	-- ^c
2	DMF	Pd ₂ dba ₃ + 4PPh ₃	Et ₃ N	0.08	2.0	80
3	DMF	Pd ₂ dba ₃ + 4PPh ₃	Et ₃ N	0.16	1.2	80
4	Et ₃ N	Pd ₂ dba ₃ + 4PPh ₃	-	0.16	1.2	80
5	Et ₃ N	Pd(OAc) ₂ + 2PPh ₃	-	0.16	1.2	77
6	Et ₂ NH	Pd(OAc) ₂ + 2PPh ₃	-	0.16	1.2	85
7	Et ₂ NH	Pd ₂ dba ₃ + 4PPh ₃	-	0.16	1.2	80

^a 1.5 equiv. of amine to **2a** was used. ^b Isolated yield based on **2a** used. ^c Most of **2a** remained unchanged.


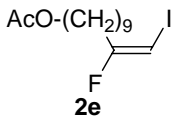
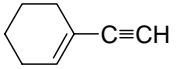
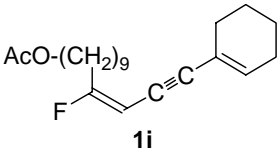
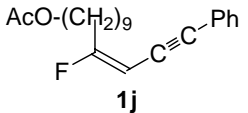
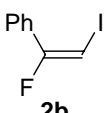
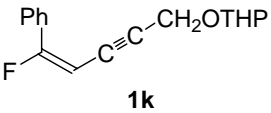
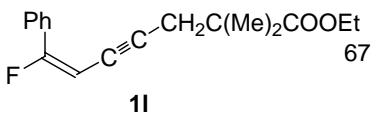
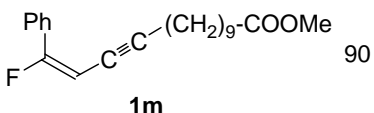
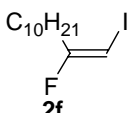
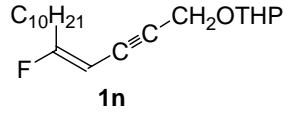
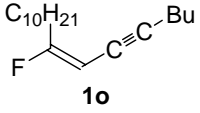
Under the reaction conditions, various (*E*)-1-fluoro-1,3-enynes (**1**) could be stereoselectively prepared (*E* / *Z* ≥ 98 / 2) from (*E*)-2-fluoro-1-iodoalk-1-enes (**2**) and alk-1-ynes as shown in Table 2. As both the preparation of **2** and the cross-coupling reaction proceed under mild conditions, the introduction of various functional groups into fluoroenynes (**1**) is possible.

Table 2. Stereoselective synthesis of (*E*)-fluoroenynes **1**

Entry		Alkyne	Product	Yield / % ^a
1		Bu-C≡CH		85
2	2c	TMS-C≡CH		80
3	2c	Ph-C≡CH		84
4	2c	THPOCH ₂ -C≡CH		88
5	2c	EtOOC(Me) ₂ CH ₂ -C≡CH		77
6		TMS-C≡CH		92
7	2d	AcO-(CH ₂) ₉ -C≡CH		78
8	2d	Ph-C≡CH		84

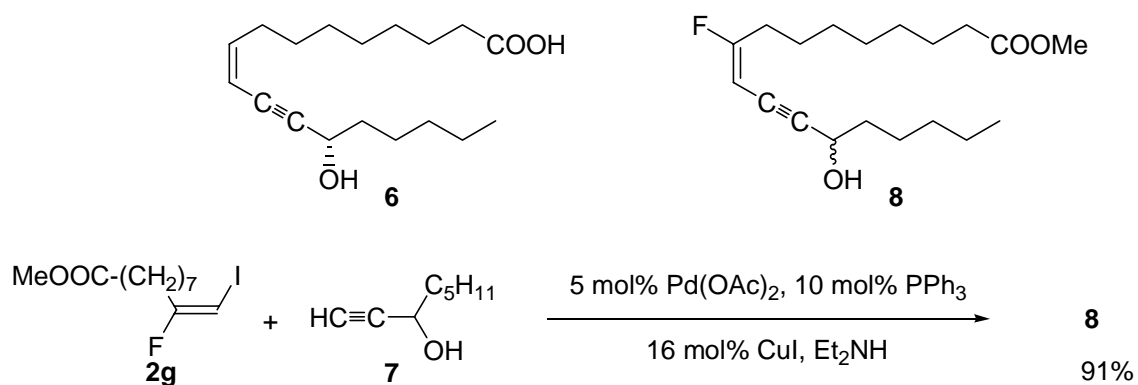
If not otherwise mentioned, the reaction was carried out at room temperature for 12 h. ^a Isolated yield based on **2**.

Table 2. (Continued)

Entry		Alkyne	Product	Yield / % ^a
9	 2e		 1i	78
10	2e	Ph-C≡CH	 1j	84
11	 2b	THPOCH ₂ -C≡CH	 1k	85
12	2b	EtOOC(Me) ₂ CH ₂ -C≡CH	 1l	67
13 ^b	2b	MeOOC-(CH ₂) ₉ -C≡CH	 1m	90
14	 2f	THPOCH ₂ -C≡CH	 1n	90
15	2f	Bu-C≡CH	 1o	78

^b The reaction was carried out at room temperature for 2.5 days.

In order to show the usefulness of this method, a fluorinated analog of a biologically active compound was synthesized. Recently, 11,12-dehydrocoriolic acid (**6**) was found to have stronger inhibitory activity against rice blast fungus than natural coriolic acid.¹¹ The author planned to synthesize a fluorinated analog of the dehydrocoriolic acid using this method. The coupling reaction of methyl (*E*)-9-fluoro-10-iododec-9-enoate (**2g**)⁷ with oct-1-yn-3-ol (**7**) was carried out to provide the (±)-9-fluorodehydrocoriolic acid methyl ester (**8**) in 91% yield directly (Scheme 1).



Scheme 1.

Conclusion

The stereoselective synthesis of (*E*)-1-fluoro-1,3-enynes was carried out by Pd-catalyzed cross-coupling reaction of (*E*)-2-fluoro-1-iodoalk-1-enes with alk-1-ynes. As the reaction proceeds under mild conditions, a variety of polyfunctionalized 1-fluoro-1,3-enynes could be prepared. By this method, a fluorinated analog of a biologically active compound, (\pm)-9-fluorodehydrocoriolic acid methyl ester, was stereoselectively obtained in good yield.

Experimental

General

The IR spectra were recorded using a JASCO FT/IR-410. The ^1H NMR (400 MHz) and ^{19}F NMR (376 MHz) spectra were recorded in CDCl_3 on a JEOL JNM-A400II FT NMR and the chemical shifts, δ , are referred to TMS (^1H) and CFCl_3 (^{19}F), respectively. The EI-low and high-resolution mass spectra were measured on a JEOL JMS-700TZ, JMS-FABmate or JMS-HX110. The elemental micro-analyses were done using a Yanagimoto CHN Corder MT-5. (Trimethylsilyl)acetylene, $\text{Pd}(\text{OAc})_2$, Pd_2dba_3 , PPh_3 , hex-1-yne, phenylacetylene, propargyl alcohol and eth-1-ynylcyclohexenol were purchased from Tokyo Kasei Co. Ltd.. Propargyl alcohol was converted to the THP ether according to the literature.¹² Eth-1-ynylcyclohexene¹³ and oct-1-yn-3-ol¹³ were prepared according to the literature. Ethyl 2,2-dimethylpent-4-ynoate was prepared from ethyl isobutyrate and propargyl bromide.¹⁴ Preparation of $\text{Et}_3\text{N}\cdot 5\text{HF}$ was shown in Chapter 1. The procedures for the preparation of (*E*)-fluoroalkenyliodonium salts (**1**) and (*E*)-2-fluoro-1-iodoalk-1-enes (**2**) were also shown in Chapter 1. Preparation of acetoxyundec-10-yne was described in Chapter 4.

For the spectrum information of fluoroiodoalkenes (**2b,c,d,f**), see Chapter 1. For the spectrum information of (*E*)-11-acetoxy-2-fluoro-1-iodo-undec-1-ene (**2e**), see Chapter 4.

Cross-coupling reaction of hex-1-yne with **3a**.

A mixture of PPh_3 (26 mg, 0.1 mmol) and $\text{Pd}(\text{OAc})_2$ (11 mg, 0.05 mmol) in DMF (10 mL) was stirred at room temperature under an atmosphere of nitrogen for 10 min. To the reaction mixture, hex-1-yne (98 mg, 1.2 mmol), fluoroalkenyliodonium salt (**3a**) prepared from methyl undec-10-ynoate (196 mg, 1 mmol), Et_3N (150 mg, 1.5 mmol), and CuI (15 mg, 0.08 mmol) were successively added. The mixture was stirred at

room temperature overnight and then poured into an aqueous NH_4Cl solution (20 mL). The mixture was extracted with ether (20 mL \times 3) and the organic phase was dried over MgSO_4 . Purification by column chromatography (silica gel/hexane-ether) gave methyl (*E*)-10-fluoroheptadec-10-en-12-ynoate (**1a**) in 59% yield with 41% of *p*-tolylhexyne (**5**).

Cross-coupling reaction of alk-1-yne with 2-fluoro-1-iodoalk-1-ene (**2**)

Methyl (*E*)-10-fluoroheptadec-10-en-12-ynoate (**1a**).

A mixture of methyl (*E*)-11-iodo-10-fluoroundec-10-enoate (**2c**) (342 mg, 1 mmol), PPh_3 (26.2 mg, 0.1 mmol), $\text{Pd}(\text{OAc})_2$ (11.3 mg, 0.05 mmol), CuI (32 mg, 0.16 mmol) and hex-1-yne (98 mg, 1.2 mmol) in Et_2NH (10 mL) was stirred overnight at room temperature under atmosphere of nitrogen. The reaction mixture was poured into an aqueous NH_4Cl (20 mL) and extracted with ether (20 mL \times 3). The organic phase was dried over MgSO_4 and concentrated under reduced pressure. Purification by column chromatography (silica gel/hexane-ether) gave **1a** in 85% yield as a pale yellow oil:

IR (neat): 1741 (C=O) cm^{-1} . ^1H NMR δ =5.16 (1H, dt, J =14.0, 2.2 Hz), 3.67 (3H, s), 2.43 (2H, dt, J =22.0, 7.3 Hz), 2.31 (2H, t, J =7.3 Hz), 1.64-1.32 (18H, m), 0.92 (3H, t, J =7.3 Hz). ^{19}F NMR δ =-98.65 (1F, dt, J =14.0, 22.0 Hz). HRMS (EI) Calcd for $\text{C}_{18}\text{H}_{29}\text{FO}_2$ 296.2151, Found 296.2146.

Methyl (*E*)-10-fluoro-13-(trimethylsilyl)-tridec-10-en-12-ynoate (**1b**).

Pale yellow oil: IR (neat): 2142 (C \equiv C), 1742 (C=O) cm^{-1} . ^1H NMR δ =5.21 (1H, d, J =14.2 Hz), 3.67 (3H, s), 2.47 (2H, dt, J =22.0, 7.3 Hz), 2.31 (2H, t, J =7.6 Hz), 1.64-1.53 (4H, m), 1.32 (8H, brs), 0.18 (9H, s). ^{19}F NMR δ =-92.74 (1F, dt, J =14.2, 22.0 Hz). HRMS (EI) Calcd for $\text{C}_{17}\text{H}_{29}\text{FO}_2\text{Si}$ 312.1921, Found 312.1927.

Methyl (*E*)-10-fluoro-13-phenyltridec-10-en-12-ynoate (1c).

Pale yellow oil: IR (neat): 2209 (C C), 1739 (C=O) cm^{-1} . ^1H NMR δ =7.42-7.39 (2H, m), 7.33-7.30 (3H, m), 5.41 (1H, d, J =13.9 Hz), 3.66 (3H, s), 2.54 (2H, dt, J =22.0, 7.4 Hz), 2.28 (2H, t, J =7.6 Hz), 1.62-1.55 (4H, m), 1.38-1.31 (8H, m). ^{19}F NMR δ =-93.34 (1F, dt, J =13.9, 22.0 Hz). HRMS (EI) Calcd for $\text{C}_{20}\text{H}_{25}\text{FO}_2$ 316.1838, Found 316.1844.

Methyl (*E*)-10-fluoro-14-(2-tetrahydropyranyloxy)-tetradec-10-en-12-ynoate (1d).

Pale yellow oil: IR (neat): 2220 (C C), 1740 (C=O) cm^{-1} . ^1H NMR δ =5.22 (1H, dt, J =13.9, 2.2 Hz), 4.82 (1H, t, J =3.4 Hz), 4.44-4.33 (2H, m), 3.88-3.82 (1H, m), 3.67 (3H, s), 3.56-3.45 (1H, m), 2.45 (2H, dt, J =21.9, 7.3 Hz), 2.30 (2H, t, J =7.6 Hz), 1.87-1.53 (10H, m), 1.31 (8H, brs). ^{19}F NMR δ =-93.50 (1F, dt, J =13.9, 21.9 Hz). HRMS (EI) Calcd for $\text{C}_{20}\text{H}_{31}\text{FO}_4$ 354.2206, Found 354.2203.

Ethyl (*E*)-7-fluoro-15-methoxycarbonyl-2,2-dimethylpentadec-6-en-4-ynoate (1e).

Pale yellow oil: IR (neat): 1735 (C=O) cm^{-1} . ^1H NMR δ =5.16 (1H, dt, J =13.9, 2.2 Hz), 4.14 (2H, q, J =7.1 Hz), 3.67 (3H, s), 2.56 (2H, s), 2.42 (2H, dt, J =22.2, 7.6 Hz), 2.30 (2H, t, J =7.6 Hz), 1.64-1.52 (4H, m), 1.31-1.24 (17H, m). ^{19}F NMR δ =-96.62 (1F, dt, J =13.9, 22.2 Hz). HRMS (EI) Calcd for $\text{C}_{21}\text{H}_{33}\text{FO}_4$ 368.2363, Found 368.2356.

(*E*)-13-Chloro-4-fluoro-1-(trimethylsilyl)-tridec-3-en-1-yne (1f).

Pale yellow oil: IR (neat): 2142 (C C), 1656 (C=C) cm^{-1} . ^1H NMR δ =5.21 (1H, d, J =13.9 Hz), 3.53 (2H, t, J =6.6 Hz), 2.48 (2H, dt, J =21.4, 7.3 Hz), 1.81-1.74 (2H, m), 1.61-1.32 (12H, m), 0.19 (9H, s). ^{19}F NMR δ =-92.71 (1F, dt, J =13.9, 21.4 Hz). Anal. C, 63.44; H, 9.32. Found: C, 63.68; H, 9.22.

(E)-1-Acetoxy-22-chloro-13-fluorodocos-12-en-10-yne (1g).

Pale yellow oil: IR (neat): 1741 (C=O), 1239 (C-OR) cm^{-1} . ^1H NMR δ =5.16 (1H, dt, J =14.4, 2.2 Hz), 4.05 (2H, t, J =6.8 Hz), 3.53 (2H, t, J =6.8 Hz), 2.44 (2H, dt, J =22.2, 7.4 Hz), 2.30 (2H, t, J =6.8 Hz), 2.04 (3H, s), 1.80-1.73 (2H, m), 1.65-1.31 (26H, m). ^{19}F NMR δ =-97.67 (1F, dt, J =14.4, 22.2 Hz). HRMS (EI) Calcd for $\text{C}_{24}\text{H}_{40}\text{ClFO}_2$ 414.2701, Found 414.2715.

(E)-13-Chloro-4-fluoro-1-phenyltridec-3-en-1-yne (1h).

Pale yellow oil: IR (neat): 2207 (C C), 1489 (C=C) cm^{-1} . ^1H NMR δ =7.42-7.39 (2H, m), 7.33-7.29 (3H, m), 5.41 (1H, d, J =13.9 Hz), 2.54 (2H, dt, J =22.0, 7.3 Hz), 2.43 (2H, t, J =7.3 Hz), 1.64-1.49 (2H, m), 1.36-1.21 (2H, m), 1.11 (10H, brs). ^{19}F NMR δ =-93.32 (1F, dt, J =13.9, 22.0 Hz). HRMS (EI) Calcd for $\text{C}_{19}\text{H}_{24}\text{ClF}$ 306.1551, Found 306.1542.

(E)-1-Acetoxy-10-fluoro-13-(1-cyclohexenyl)-tridec-10-en-12-yne (1i).

Pale yellow oil: IR (neat): 1741 (C=O), 1238 (C-OR) cm^{-1} . ^1H NMR δ =6.05-6.07 (1H, m), 5.30 (1H, d, J =14.2 Hz), 4.05 (2H, t, J =6.8 Hz), 2.46 (2H, dt, J =21.9, 7.3 Hz), 2.13-2.10 (4H, m), 2.04 (3H, s), 1.67-1.53 (8H, m), 1.31 (10H, brs). ^{19}F NMR δ =-95.41 (1F, dt, J =14.2, 21.9 Hz). HRMS (EI) Calcd for $\text{C}_{21}\text{H}_{31}\text{FO}_2$ 334.2308, Found 334.2324.

(E)-1-Acetoxy-10-fluoro-13-phenyltridec-10-en-12-yne (1j).

Pale yellow oil: IR (neat): 1739 (C=O), 1240 (C-OR) cm^{-1} . ^1H NMR δ =7.42-7.39 (2H, m), 7.33-7.26 (3H, m), 5.41 (1H, d, J =13.9 Hz), 4.03 (2H, t, J =6.8 Hz), 2.55 (2H, dt, J =21.9, 7.3 Hz), 2.03 (3H, s), 1.68-1.56 (4H, m), 1.38-1.30 (10H, m). ^{19}F NMR δ =-93.29 (1F, dt, J =13.9, 21.9 Hz). HRMS (EI) Calcd for $\text{C}_{21}\text{H}_{27}\text{FO}_2$ 330.1995, Found 330.1991.

(E)-1-Fluoro-1-phenyl-5-(2-tetrahydropyranyloxy)-pent-1-en-3-yne (1k).

Pale yellow oil: IR (neat): 2216 (C C) cm^{-1} . ^1H NMR δ =8.01-7.98 (2H, m), 7.43-7.33 (3H, m), 5.62 (1H, dt, J =2.4, 17.6 Hz), 4.85 (1H, t, J =3.6 Hz),

4.51-4.41 (2H, m), 3.89-3.83 (1H, m), 3.56-3.53 (1H, m), 1.89-1.51 (6H, m).
 ^{19}F NMR δ =-102.19 (1F, d, J =17.6 Hz). HRMS (EI) Calcd for $\text{C}_{16}\text{H}_{17}\text{FO}_2$
260.1212, Found 260.1206.

Ethyl (*E*)-7-fluoro-2,2-dimethyl-7-phenylhept-6-en-4-ynoate (1l).

Pale yellow oil: IR (neat): 1731 (C=O) cm^{-1} . ^1H NMR δ =8.02-7.98 (2H, m),
7.42-7.38 (3H, m), 5.59 (1H, dt, J =18.1, 2.7 Hz), 4.14 (2H, q, J =7.2 Hz), 2.66
(2H, s), 1.30 (6H, s), 1.23 (3H, t, J =7.2 Hz). ^{19}F NMR δ =-105.34 (1F, d,
 J =18.1 Hz). HRMS (EI) Calcd for $\text{C}_{17}\text{H}_{19}\text{FO}_2$ 274.1369, Found 274.1397.

Methyl (*E*)-13-fluoro-13-phenyltridec-12-en-10-ynoate (1m).

Pale yellow oil: IR (neat): 2215 (C C), 1739 (C=O) cm^{-1} . ^1H NMR
 δ =8.03-8.01 (2H, m), 7.42-7.38 (3H, m), 5.59 (1H, dt, J =18.3, 2.4 Hz), 3.66
(3H, s), 2.38-2.42 (2H, m), 2.29 (2H, t, J =7.6 Hz), 1.63-1.54 (4H, m),
1.42-1.40 (2H, m), 1.31 (6H, brs). ^{19}F NMR δ =-106.34 (1F, d, J =18.3 Hz).
HRMS (EI) Calcd for $\text{C}_{20}\text{H}_{25}\text{FO}_2$ 316.1838, Found 316.1824.

(*E*)-5-Fluoro-1-(2-tetrahydropyranyloxy)-pentadec-4-en-2-yne (1n).

Pale yellow oil: IR (neat): 2220 (C C), 1664 (C=C) cm^{-1} . ^1H NMR δ =5.21
(1H, dt, J =14.0, 2.4 Hz), 4.82 (1H, t, J =3.4 Hz), 4.44-4.33 (2H, m), 3.88-3.83
(1H, m), 3.56-3.45 (1H, m), 2.46 (2H, dt, J =22.0, 7.3 Hz), 1.88-1.52 (8H, m),
1.31-1.20 (14H, m), 0.88 (3H, t, J =6.6 Hz). ^{19}F NMR δ =-93.47 (1F, dt, J =14.0,
22.0 Hz). HRMS (EI) Calcd for $\text{C}_{20}\text{H}_{33}\text{FO}_2$ 324.2464, Found 324.2451.

(*E*)-8-Fluorooctadec-7-en-5-yne (1o).

Pale yellow oil: IR (neat): 2227 (C \equiv C), 1666 (C=C) cm^{-1} . ^1H NMR δ =5.16 (1H,
dt, J =14.6, 2.2 Hz), 2.43 (2H, dt, J =22.0, 7.3 Hz), 2.29-2.32 (2H, m),
1.69-1.19 (20H, m), 0.92 (3H, t, J =7.1 Hz), 0.88 (3H, t, J =7.1 Hz). ^{19}F NMR
 δ =-97.66 (1F, dt, J =14.6, 22.0 Hz). HRMS (EI) Calcd for $\text{C}_{18}\text{H}_{31}\text{F}$ 266.2410,
Found 266.2408.

Methyl (*E*)-9-fluoro-10-iododec-9-enoate (2g).

Pale yellow oil: IR (neat): 1739 (C=O), 1650 (C=C) cm^{-1} . ^1H NMR δ =5.69 (1H, d, J =17.8 Hz), 3.67 (3H, s), 2.50 (2H, dt, J =22.4, 7.3 Hz), 2.31 (3H, t, J =7.6 Hz), 1.65-1.51 (4H, m), 1.38-1.21 (6H, brs). ^{19}F NMR δ =-82.53 (1F, dt, J =17.8, 22.4 Hz). HRMS (EI) Calcd for $\text{C}_{10}\text{H}_{15}\text{FIO}$ ($\text{M}^+\text{-OMe}$) 297.0152, Found 297.0162.

(*E*)-9-Fluoro-11,12-dehydrocoriolic acid methyl ester (8).

Pale yellow oil: IR (neat): 3436 (C-OH), 2219 (C \equiv C), 1731 (C=O) cm^{-1} . ^1H NMR δ =5.21 (1H, dd, J =14.1, 2.0 Hz), 4.49 (1H, dt, J =1.4, 6.6 Hz), 3.67 (3H, s), 2.45 (2H, dt, J =22.2, 7.1 Hz), 2.38 (1H, brs), 2.31 (2H, t, J =7.6 Hz), 1.73-1.30 (18H, m), 0.90 (3H, t, J =6.8 Hz). ^{19}F NMR δ =-94.20 (1F, dt, J =14.1, 22.2 Hz). HRMS (EI) Calcd for $\text{C}_{19}\text{H}_{31}\text{FO}_3$ 326.2257, Found 326.2258. Anal. C, 69.91; H, 9.57. Found: C, 69.96; H, 9.52.

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Chapter 7

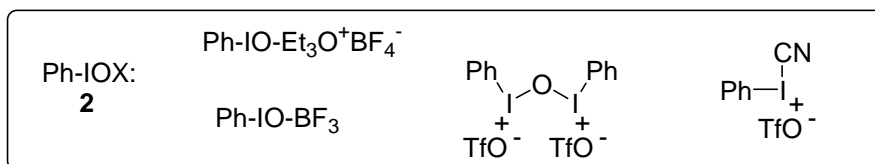
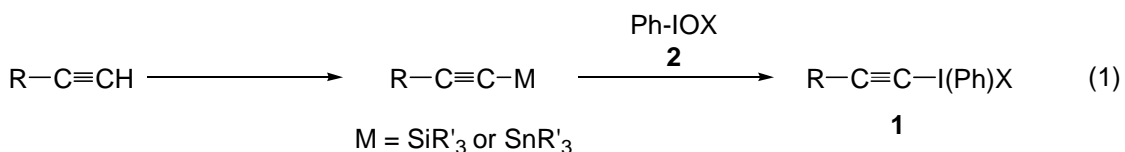
Direct Synthesis of Alkynyl(phenyl)iodonium Salts from Alk-1-yne

Abstract

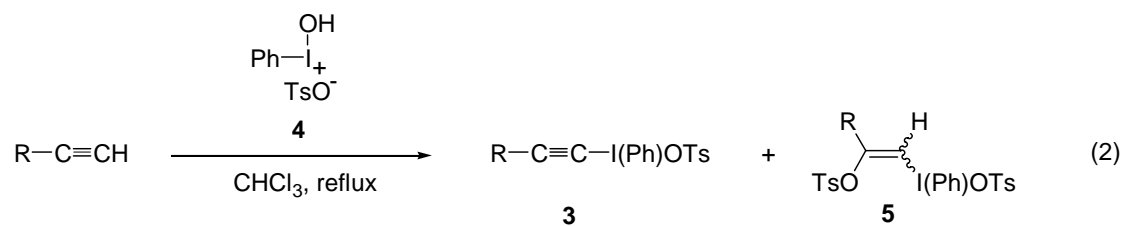
Alkynyl(phenyl)iodonium salts were directly prepared from alk-1-yne by the reaction with iodosylbenzene, aq. HBF_4 and a catalytic amount of HgO . The reaction smoothly proceeded at room temperature to give a variety of alkynyliodonium salts in good yields.

Introduction

Alkynyl(phenyl)iodonium salts (**1**) have been recently used as a versatile reagent for organic synthesis.¹ They are generally prepared from alk-1-ynes in two-steps: the transformation of alk-1-ynes to the corresponding alkynylsilanes or -stannanes, followed by the reaction of the alkynyl metals with iodosylbenzene derivatives (**2**) [Eq. (1)].³

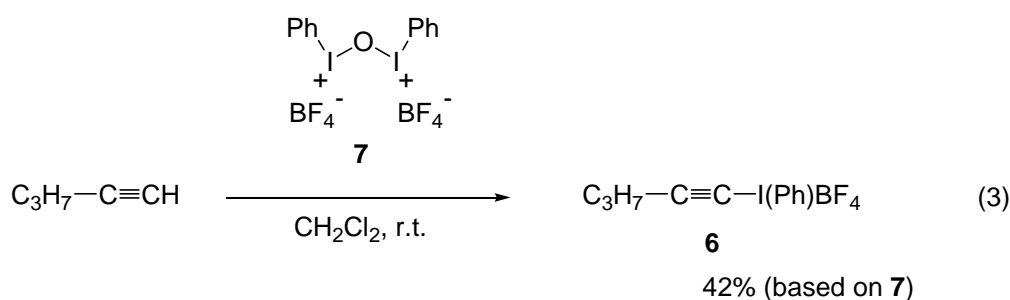


Direct conversion of alk-1-ynes to **1** is more efficient and desirable, and has been studied by many chemists.⁴ However, the direct synthetic methods are applicable only for the synthesis of aryl or sterically hindered alkyl group-substituted alkynyliodonium salts, and in other cases, the competitive formation of alkenyliodonium salts is a serious problem. For example, Koser *et al.* reported that phenyl or *t*-butylacetylene could be directly converted to the corresponding alkynyliodonium salts (**3**) using hydroxy(tosyloxy)iodobenzene (**4**); however, in the case of *i*-butyl or *n*-butylacetylene, a significant amount of β -tosyloxyalkenyliodonium salts (**5**) was formed [Eq. (2)].^{4a,b}



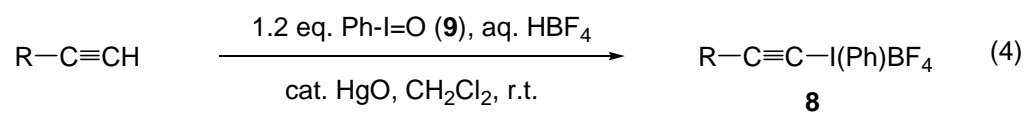
R	Alkyne / Ph-I(OTs)OH	Yield / %		R	Alkyne / Ph-I(OTs)OH	Yield / %	
		3	5			3	5
Ph	6.0 eq.	61	0	ⁱ Bu	2.6 eq.	33	29
^t Bu	3.6 eq.	74	0	ⁿ Bu	2.2 eq.	0	52

Caple *et al.* reported the direct preparation of pentyl(phenyl)iodonium tetrafluoroborate (**6**) from pent-1-yne and iodosobenzene tetrafluoroborate (**7**) [Eq. (3)].⁵ However, a serious disadvantage of their method is the use of a large excess of pentyne (*ca.* 40 times) to **7** and the synthesis of no other alkynyliodonium salts was not shown. Therefore, the two-step methodology has been the sole way for the synthesis of the alkynyliodonium salts with a normal alkyl group.



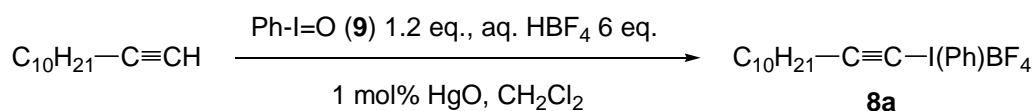
The author succeeded in the direct synthesis of alkynyliodonium salts (**8**) having a normal alkyl chain from the corresponding alk-1-ynes by the reaction with iodosylbenzene (**9**), aq. HBF₄ and a catalytic amount of HgO [Eq. (4)]. The reaction smoothly proceeded at room temperature to give **8** in good yields, and the formation of alkenyliodonium salts was not observed at all. The details of the direct synthetic methodology for the

alkynyliodonium salt are described in this chapter.



Results and Discussion

To a dichloromethane suspension (2 mL) of iodosylbenzene (**9**) (0.6 mmol) were added a 42% aq. HBF₄ (3 mmol) and HgO (0.005 mmol) to give two liquid phases, a clear organic phase and a clear yellow aqueous phase. To the reaction mixture was added dodec-1-yne (0.5 mmol) at room temperature, and the yellow color of the aqueous phase faded after vigorous stirring for 30 min. The formation of dodec-1-ynyl(phenyl)iodonium tetrafluoroborate (**8a**), and the absence of the dodec-1-yne and alkenyliodonium salts could be confirmed from the ¹H NMR spectrum of the mixture (Scheme 2).



Scheme 2.

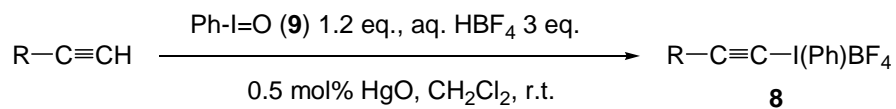
The reaction conditions were optimized as shown in Table 1. Although the amount of HgO could be reduced to 0.01 mol% (1/10,000 equivalent to dodec-1-yne), the reaction scarcely proceeded without it (Entry 6). On the contrary, too much HgO promoted the oxymercuration of dodecyne and dodecan-2-one was formed (Entry 1). When the reaction was carried out with 0.5 mol% of HgO and 3 eq. of aq. HBF₄, the best result was obtained as shown in Entry 9.


Table 1. Reaction condition for direct synthesis of dodec-1-ynyliodonium salt (**8a**)

$C_{10}H_{21}-C\equiv CH$	$\xrightarrow[\text{cat. HgO, CH}_2\text{Cl}_2, \text{r.t.}]{\text{Ph-I=O (9), aq. HBF}_4}$		$C_{10}H_{21}-C\equiv C-I(\text{Ph})\text{BF}_4$	
			8a	
Entry	aq. HBF ₄ / eq.	HgO / mol%	Time / min	Yield of 8a / % ^a
1	6	3	10	68
2	6	1	20	70
3	6	0.5	30	73
4	6	0.1	80	70
5	6	0.01	8 hours	71
6	6	0	5 days	14 ^b
7	3	1	40	73
8	1.2	1	18 hours	67
9	3	0.5	40	76

^a Isolated yield based on dodec-1-yne used. ^b Significant amount of dodec-1-yne remained.

A variety of alk-1-yne were subjected to the reaction to synthesize alkynyliodonium salts (**8b-i**) (Table 2). Alkynes having a normal alkyl or a sterically hindered group can be converted to the alkynyliodonium salts in good yields. Phenylacetylene also gave the corresponding alkynyliodonium salt, phenylethynyl(phenyl)iodonium tetrafluoroborate (**8i**); however, the product **8i** was unstable under the reaction conditions and the yield was relatively low (Entry 9). The introduction of various functional groups, e.g., Cl, ^tBuCO, COOMe, AcO, was also possible (Entries 5,6,7 and 8).

Table 2. Direct synthesis of alkynyl(phenyl)iodonium salts (**8**)

Entry	Product	Time / min.	Yield / % ^a
1	$\text{C}_{10}\text{H}_{21}-\text{C}\equiv\text{C}-\text{I}(\text{Ph})\text{BF}_4$ 8a	30	76
2	$\text{}^t\text{Bu}-\text{C}\equiv\text{C}-\text{I}(\text{Ph})\text{BF}_4$ 8b	40	86
3	$\text{Bu}-\text{C}\equiv\text{C}-\text{I}(\text{Ph})\text{BF}_4$ 8c	30	58
4	 - $\text{CH}_2-\text{C}\equiv\text{C}-\text{I}(\text{Ph})\text{BF}_4$ 8d	60	78
5	$\text{Cl}-(\text{CH}_2)_9-\text{C}\equiv\text{C}-\text{I}(\text{Ph})\text{BF}_4$ 8e	30	80
6	$\text{}^t\text{Bu}-\text{CO}-(\text{CH}_2)_8-\text{C}\equiv\text{C}-\text{I}(\text{Ph})\text{BF}_4$ 8f	15	79
7	$\text{MeOOC}-(\text{CH}_2)_8-\text{C}\equiv\text{C}-\text{I}(\text{Ph})\text{BF}_4$ 8g	15	78
8	$\text{AcO}-(\text{CH}_2)_9-\text{C}\equiv\text{C}-\text{I}(\text{Ph})\text{BF}_4$ 8h	30	70
9	$\text{Ph}-\text{C}\equiv\text{C}-\text{I}(\text{Ph})\text{BF}_4$ 8i	10	48

^a Isolated yield based on alkyne used.

Reaction mechanism

The reaction mechanism of the formation of alkynyliodonium salts (**1**) from alk-1-yne with iodosylbenzene (**9**), HBF_4 and HgO is not well understood yet, but a plausible mechanism is illustrated in Figure 1.^{2,3a} Initially, alk-1-yne reacted with HgO to produce an alkynylmercury intermediate (**10**). Then, the intermediate (**10**) attacked the **9** activated by HBF_4 to produce **8** and $\text{Hg}(\text{OH})_2$. Elimination of H_2O from the $\text{Hg}(\text{OH})_2$ regenerated HgO .

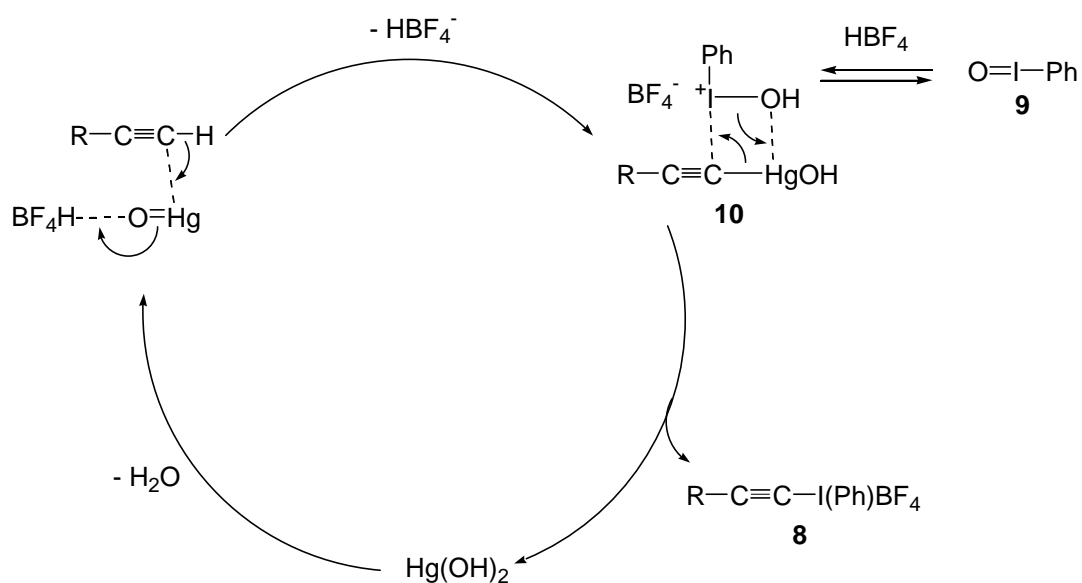


Figure 1.

Conclusion

Alkynyliodonium salts having a normal alkyl or a sterically hindered group can be directly obtained from the corresponding alk-1-yne. The introduction of various functional groups, such as Cl, ^tBuCO, COOMe, AcO, was also possible.

Experimental

General

IR spectra were recorded using a JASCO FT/IR-410. ^1H NMR (400 MHz), ^{19}F NMR (376 MHz) and ^{13}C -NMR (100 MHz) spectra were recorded in CDCl_3 on a JEOL JNM-A400II FT NMR and chemical shifts, δ , are referred to TMS (^1H , ^{13}C) and CFCl_3 (^{19}F). EI low- and high-resolution mass spectra were measured on a JEOL JMS-700TZ, JMS-FABmate or JMS-HX110. Elemental microanalyses were done using a Yanagimoto CHN Corder MT-5. 3,3-Dimethylbut-1-yne⁶ was prepared according to the literatures. Phenylacetylene and hex-1-yne were purchased from Tokyo Kasei Co., Ltd., and used without further purification. HgO and aq. HBF_4 were purchased from Wako Chemical Co., Inc.. Preparation of dodec-1-yne, 3-cyclohexylprop-1-yne, 11-chloroundec-1-yne, methyl undec-10-ynoate and 2,2-dimethyltridec-12-yn-3-one were shown in Chapter 1. Preparation of acetoxyundec-10-yne was described in Chapter 4.

For the spectrum information of 2-phenyleth-1-ynyl(phenyl)iodonium tetrafluoroborate (**8i**), see ref. 2.

Synthesis of alk-1-ynyl(phenyl)iodonium tetrafluoroborate (**1**)

Typical experimental procedure: To a CH_2Cl_2 suspension (2 mL) of iodosylbenzene (**9**) (132 mg, 0.6 mmol) were added 42% aqueous solution of HBF_4 (7.2 mL, 3 mmol) and HgO (0.54 mg, 0.0025 mmol) at room temperature, and the mixture was stirred for a few minutes until the solid part dissolved completely. To the resulting mixture, dodec-1-yne (83 mg, 0.5 mmol) was added and the mixture was stirred at room temperature until the yellow color of the aqueous phase disappeared. Then the mixture was poured into a 5% aqueous solution of NaBF_4 (20 mL, 1 mmol) and the separated aqueous phase was extracted with CH_2Cl_2 (10 mL \times 3). The combined organic phases were dried over MgSO_4 and concentrated

under reduced pressure. The product was solidified by dissolving the resulting viscous liquid in a little CH₂Cl₂ (2 mL), followed by the addition of a large quantity of hexane (40 mL). The liquid part was removed by decantation, and the remained solid was washed with hexane. Finally, the solvent was removed completely under reduced pressure to give dodec-1-ynyl(phenyl)iodonium tetrafluoroborate (**8a**) (76%, 173 mg, 0.38 mmol).

Dodec-1-ynyl(phenyl)iodonium tetrafluoroborate (8a).

M.p. 41.5-42.2 °C, $\delta_{\text{H}}(\text{CDCl}_3)$ 0.88 (3H, t, J 7.1 Hz, 12-H), 1.19-1.39 (14H, m), 1.55-1.63 (2H, m, 4-H), 2.65 (2H, t, J 7.1 Hz, 3-H), 7.53-8.07 (5H, m, Ph); $\delta_{\text{C}}(\text{CDCl}_3)$ 14.08, 15.95, 20.83, 22.64, 27.56, 28.73, 28.86, 29.23, 29.34, 29.46, 31.83, 114.10, 114.61, 132.69 (2C), 132.85, 133.78 (2C); $\nu(\text{KBr})/\text{cm}^{-1}$ 3051, 2924, 2853, 2168, 1470, 1441, 1069, 1038, 987, 738, 678, 650; [HR FAB-MS: Calc. for C₁₈H₂₆I ($M - \text{BF}_4$): 369.1079. Found: M⁺ - BF₄, 369.1096]. Found: C, 47.42; H, 5.81%. Calcd for C₁₈H₂₆BF₄I: C, 47.40; H, 5.75%.

3,3-Dimethylbut-1-ynyl(phenyl)iodonium tetrafluoroborate (8b).

M.p. 189.6-190.5 °C, $\delta_{\text{H}}(\text{CDCl}_3)$ 1.33 (9H, s, ^tBu), 7.55-8.05 (5H, m, Ph); $\delta_{\text{C}}(\text{CDCl}_3)$ 15.74, 29.91 (3C), 30.21, 114.75, 121.39, 132.77 (2C), 132.83, 133.50 (2C); $\nu(\text{KBr})/\text{cm}^{-1}$ 3097, 2977, 2932, 2871, 2192, 2155, 1560, 1470, 1446, 1366, 1286, 1253, 1051, 921, 743, 675, 645; [HR FAB-MS: Calc. for C₁₂H₁₄I ($M - \text{BF}_4$): 285.0140. Found: M⁺ - BF₄, 285.0146]. Found: C, 38.55; H, 3.74%. Calcd for C₁₂H₁₄BF₄I: C, 38.75; H, 3.79%.

Hex-1-ynyl(phenyl)iodonium tetrafluoroborate (8c).

M.p. 106.2-107.0 °C, $\delta_{\text{H}}(\text{CDCl}_3)$ 0.91 (3H, t, J 7.3 Hz, 6-H), 1.35-1.45 (2H, m, 5-H), 1.55-1.63 (2H, m, 4-H), 2.66 (2H, t, J 7.3 Hz, 3-H), 7.54-8.07 (5H, m, Ph); $\delta_{\text{C}}(\text{CDCl}_3)$ 13.34, 16.64, 20.55, 21.85, 29.53, 114.20, 114.75, 132.77 (2C), 132.90, 133.70 (2C); $\nu(\text{KBr})/\text{cm}^{-1}$ 3097, 2963, 2932, 2873, 2187, 1561, 1469,

1446, 1095, 740, 674, 647; [HR FAB-MS: Calc. for C₁₂H₁₄I (*M* - BF₄): 285.0140. Found: M⁺ - BF₄, 285.0141].

3-Cyclohexylprop-1-ynyl(phenyl)iodonium tetrafluoroborate (8d).

M.p. 86.2-87.2 °C, δ_H(CDCl₃) 0.94-1.30 (5H, m), 1.56-1.77 (6H, m), 2.57 (2H, d, *J* 6.6 Hz, 3-H), 7.54-8.07 (5H, m, Ph); δ_C(CDCl₃) 16.43, 25.82 (2C), 25.84, 28.50, 32.57 (2C), 36.87, 113.58, 114.83, 132.78 (2C), 132.91, 133.69 (2C); ν(KBr)/cm⁻¹ 3086, 2928, 2849, 2185, 1562, 1473, 1446, 1417, 1327, 1275, 1070, 891, 765, 738, 676, 650; [HR FAB-MS: Calc. for C₁₅H₁₈I (*M* - BF₄): 325.0453. Found: M⁺ - BF₄, 325.0470]. Found: C, 43.83; H, 4.42%. Calcd for C₁₅H₁₈BF₄I: C, 43.73; H, 4.40%.

11-Chloroundec-1-ynyl(phenyl)iodonium tetrafluoroborate (8e).

M.p. 47.7-48.4 °C, δ_H(CDCl₃) 1.21-1.44 (10H, m), 1.55-1.63 (2H, m, 4-H), 1.72-1.79 (2H, m, 10-H), 2.64 (2H, t, *J* 7.3 Hz, 3-H), 3.53 (2H, t, *J* 6.8 Hz, 11-H), 7.52-8.07 (5H, m, Ph); δ_C(CDCl₃) 15.90, 20.87, 26.77, 27.55, 28.69, 28.73, 28.77, 29.16, 32.56, 45.18, 114.15, 114.60, 132.75 (2C), 132.91, 133.77 (2C); ν(KBr)/cm⁻¹ 3050, 2992, 2925, 2854, 2166, 1562, 1470, 1441, 1305, 1051, 988, 740, 679, 650; [HR FAB-MS: Calc. for C₁₇H₂₃ClI (*M* - BF₄): 389.0533. Found: M⁺ - BF₄, 389.0545]. Found: C, 42.91; H, 4.76%. Calcd for C₁₇H₂₃BClF₄I: C, 42.85; H, 4.86%.

2-(10,10-Dimethyl-9-oxoundecanyl)ethynyl(phenyl)iodonium tetrafluoroborate (8f).

Oil, δ_H(CDCl₃) 1.13-1.37 (17H, m), 1.51-1.63 (4H, m), 2.47 (2H, t, *J* 7.1 Hz, 10-H), 2.65 (2H, t, *J* 7.1 Hz, 3-H), 7.53-8.07 (5H, m, Ph); δ_C(CDCl₃) 16.03, 20.78, 23.74, 26.37 (3C), 27.47, 28.52, 28.56, 29.03, 29.13, 36.35, 44.10, 113.96, 114.61, 132.70 (2C), 132.86, 133.75 (2C), 216.41; ν(neat)/cm⁻¹ 3093, 2930, 2857, 2182, 1702, 1469, 1445, 1366, 1067, 985, 740, 676; [HR FAB-MS: Calc. for C₂₁H₃₀IO (*M* - BF₄): 425.1341. Found: M⁺ - BF₄,

425.1344]. Found: C, 49.19; H, 5.91%. Calcd for C₂₁H₃₀BF₄IO: C, 49.25; H, 5.90%.

10-Methoxycarbonyldec-1-ynyl(phenyl)iodonium tetrafluoroborate (8g).

Oil, $\delta_{\text{H}}(\text{CDCl}_3)$ 1.21-1.35 (8H, m), 1.55-1.62 (4H, m), 2.30 (2H, t, J 7.6 Hz, 10-H), 2.65 (2H, t, J 7.1 Hz, 3-H), 3.67 (3H, s), 7.53-8.07 (5H, m, Ph); $\delta_{\text{C}}(\text{CDCl}_3)$ 16.14, 20.81, 24.73, 27.47, 28.50 (2C), 28.85 (2C), 33.98, 51.55, 114.01, 114.73, 132.76 (2C), 132.90, 133.73 (2C), 174.35; $\nu(\text{neat})/\text{cm}^{-1}$ 3092, 3068, 2931, 2856, 2180, 1734, 1469, 1444, 1065, 986, 741, 677; [HR FAB-MS: Calc. for C₁₈H₂₄IO₂ ($M - \text{BF}_4$): 399.0821. Found: $M^+ - \text{BF}_4$, 399.0832].

11-Acetoxyundec-1-ynyl(phenyl)iodonium tetrafluoroborate (8h).

M.p. 56.0-57.0 °C, $\delta_{\text{H}}(\text{CDCl}_3)$ 1.21-1.35 (10H, m), 1.56-1.63 (4H, m), 2.05 (3H, s), 2.65 (2H, t, J 7.0 Hz, 3-H), 4.05 (2H, t, J 6.8 Hz, 11-H), 7.53-8.07 (5H, m, Ph); $\delta_{\text{C}}(\text{CDCl}_3)$ 16.05, 20.83, 21.01, 25.75, 27.51, 28.49, 28.64, 28.74, 29.02, 29.14, 64.58, 113.95, 114.57, 132.69 (2C), 132.86, 133.79 (2C), 171.41; $\nu(\text{neat})/\text{cm}^{-1}$ 3100, 3068, 2927, 2851, 2189, 1695, 1563, 1472, 1371, 1266, 1065, 987, 746, 678; [HR FAB-MS: Calc. for C₁₉H₂₆IO₂ ($M - \text{BF}_4$): 413.0978. Found: $M^+ - \text{BF}_4$, 413.0968].

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Chapter 8

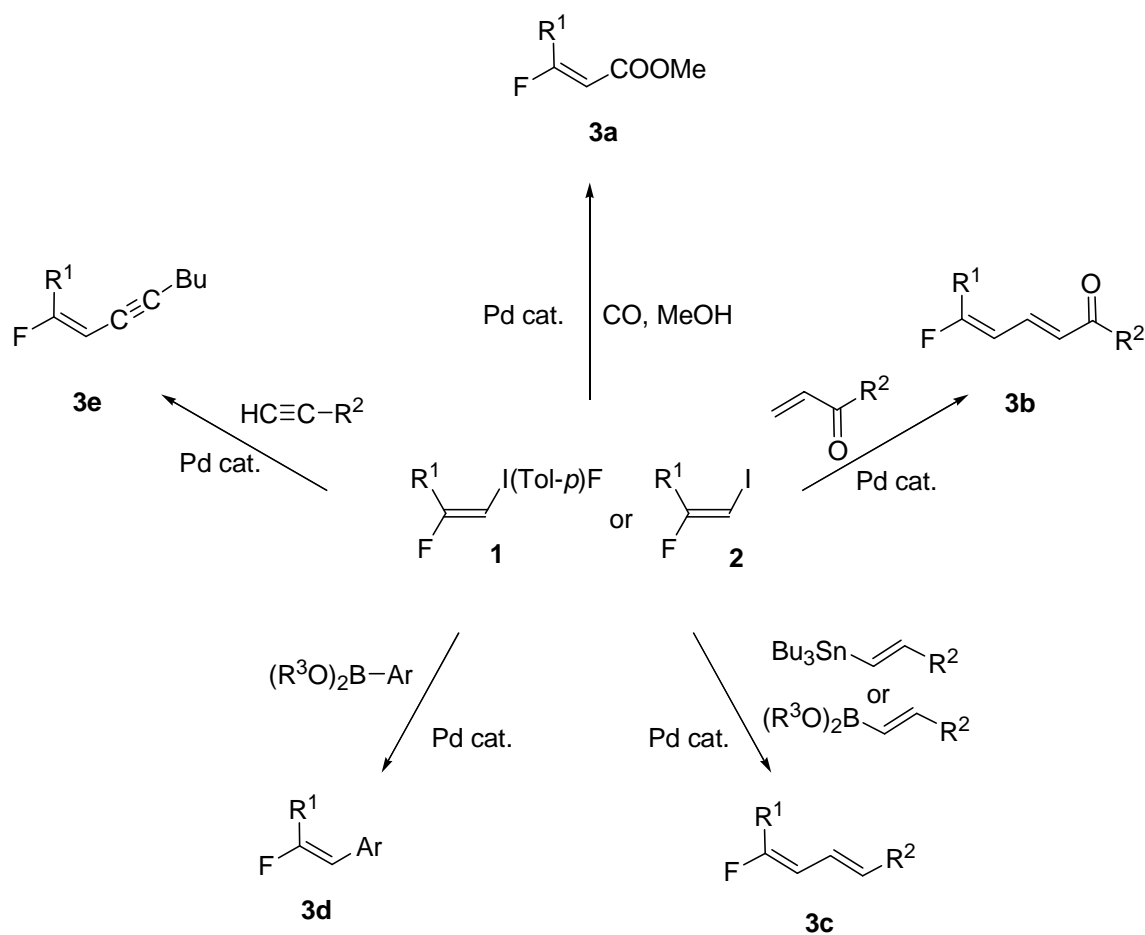
Stereoselective Synthesis of (*Z*)-2-Fluoroalk-1-enyl(phenyl)iodonium Salts and their Application to the Synthesis of (*Z*)-2-Fluoroalk-1-ene Derivatives

Abstract

Stereoselective synthesis of (*Z*)-2-fluoroalk-1-enyl(phenyl)iodonium salts was attempted by Michael-type HF-addition to alk-1-enyl(phenyl)iodonium salts using Et₃N·3HF or hydrofluoric acid. By Pd-catalyzed cross-coupling reactions using the fluoroalkenylidonium salts, stereoselective synthesis of (*Z*)-2-fluoroalk-1-ene derivatives was examined.

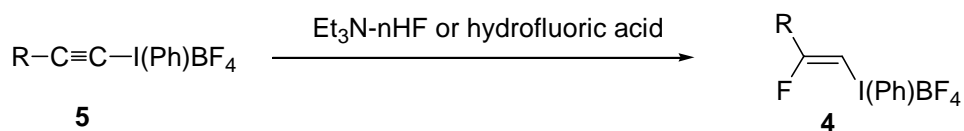
Introduction

Fluorinated analogues of natural compounds have attracted the interest of biological and medicinal chemists, because the introduction of a fluorine atom into a natural product can dramatically enhance the biological activity.¹ When a fluorine atom is introduced into a double bond of a biologically active compound, the regio- and stereoselective introduction of the fluorine atom is important because the bioactivity is strongly dependent on the position and stereochemistry of the fluorine atom.² The most popular approach to the stereoselective preparation of fluoroalkenes³ is the Horner-Wadsworth-Emmons reaction using fluoroorganophosphonates with carbonyl compounds; however, a mixture of stereoisomers is generally formed.⁴ In Chapter 1, the author presented the stereoselective synthesis of (*E*)-2-fluoroalk-1-enyl(4-methylphenyl)iodonium fluorides (**1**) and their transformation to (*E*)-2-fluoro-1-iodoalk-1-enes (**2**).^{5a} These fluoroalkenyl iodides were stereoselectively transformed to (*E*)-2-fluoroalk-1-ene derivatives (**3a-e**) in good yields by Pd-catalyzed cross-coupling reactions with CO and methanol (methoxycarbonylation, Chapter 2),^{5b} α,β -unsaturated carbonyl compounds (Heck reaction, Chapter 3),^{5c,d} organostannanes (Stille reaction, Chapter 3),^{5d} organoboranes (Suzuki-Miyaura reaction, Chapter 4)^{5e} or terminal alkynes (Sonogashira reaction, Chapter 6)^{5f} (Scheme 1). However, the stereoselective synthesis of (*Z*)-2-fluoroalk-1-ene derivatives has been unknown.



Scheme 1. Stereoselective synthesis of (*E*)-2-fluoroalk-1-ene derivatives (**3a-e**)

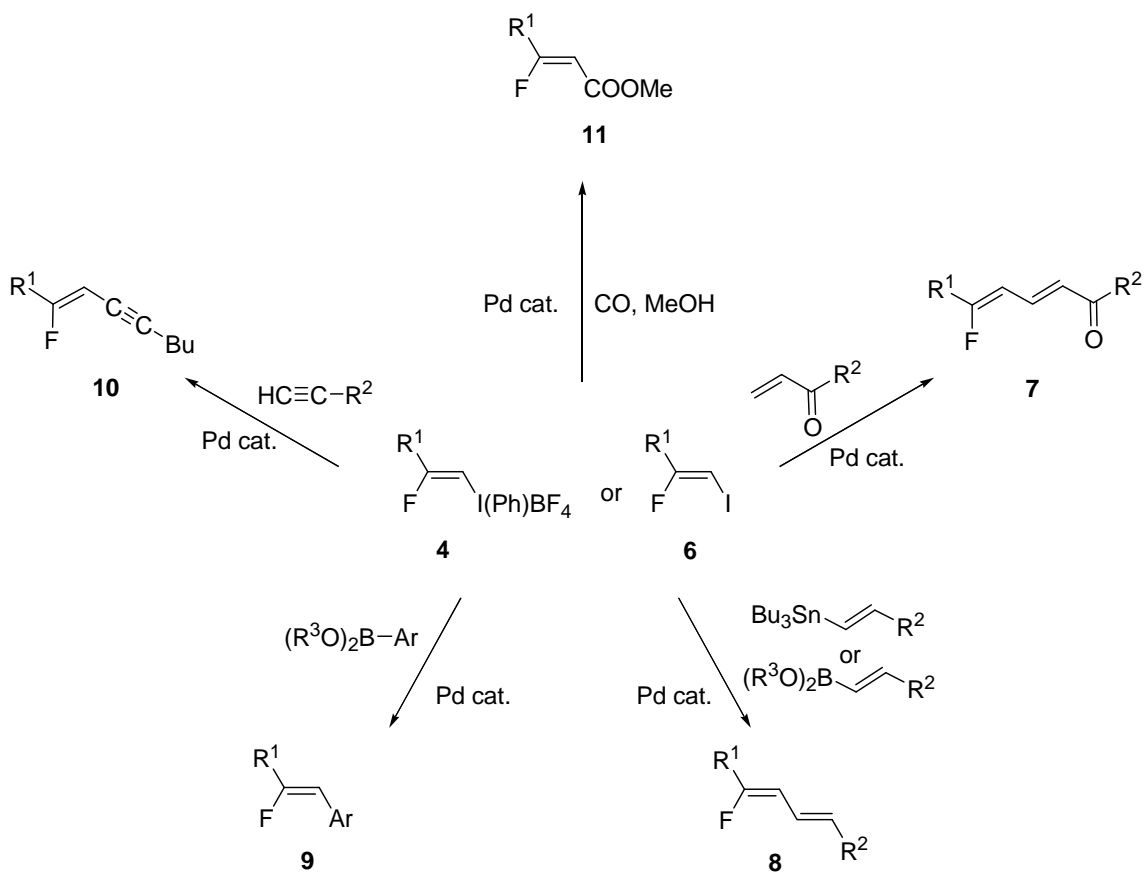
Ochiai *et al.* reported that (*Z*)-2-fluoroalk-1-enyl(phenyl)iodonium salts (**4**) were stereoselectively prepared by Michael-type addition of a fluoride anion to the corresponding alkynyliodonium salts (**5**) with CsF ; however, the yields were low (15-20%).⁶ As the reaction of **5** with metal fluorides was fruitless, the author examined $\text{Et}_3\text{N-nHF}$ ⁷ or hydrofluoric acid for the preparation of **4** (Scheme 2).⁸



Scheme 2. Synthesis of (*Z*)-2-fluoroalk-1-enyliodonium salts (**4**)

By the cross-coupling reactions using the

(*Z*)-fluoroalkenyliodonium salts (**4**), the author attempted the stereoselective synthesis of various (*Z*)-2-fluoroalk-1-ene derivatives (**6-11**) (Scheme 3).



Scheme 3. Stereoselective synthesis of (*Z*)-2-fluoroalk-1-ene derivatives (**6-11**)

Results and Discussion

Stereoselective synthesis of (*Z*)-2-fluoroalk-1-enyl(phenyl)iodonium salts (4)

Initially, an HF addition to dodec-1-ynyl(phenyl)iodonium tetrafluoroborate (**5a**) was examined using Et₃N·nHF to obtain (*Z*)-2-fluorododec-1-enyl(phenyl)iodonium tetrafluoroborate (**4a**) (Table 1). Although Et₃N·5HF was inert to **5a** in dichloromethane at room temperature (Entry 1), a more nucleophilic fluorinating reagent,⁹ Et₃N·3HF, reacted slowly with **5a** to give **4a** in 71% yield after 96 h (Entry 2). When **5a** was treated with a more nucleophilic reagent, Et₃N·2HF, in dichloromethane, further fluorination proceeded to produce 1,2,2-trifluorododecane (**12**), and the yield of **4a** was reduced to 32% (Entry 3). When the reaction of **5a** was carried out using Et₃N·3HF without dichloromethane, compound **4a** was obtained in 71% yield in 78 h (Entry 4). The reaction proceeded more effectively at higher temperature, although the formation of **12** was observed when the reaction was carried out at 60 °C (Entry 6). Hydrofluoric acid was found to be more effective than Et₃N·3HF, and **5a** was converted to **4a** in 81% yield with commercially available 46% hydrofluoric acid at 60 °C for 84 h (Entry 7). Finally, the best result was obtained by the reaction with 20% hydrofluoric acid, and **4a** was synthesized in 84% yield in 6 h (Entry 9).

The stereochemistry of **4a** was determined by ¹H NMR. A vinylic hydrogen of **4a** appeared at 6.54 ppm as a doublet (³J_{H-F} = 33.2 Hz), which was in good agreement with the reported data of (*Z*)-2-fluorodec-1-enyl(phenyl)iodonium salts.⁶

Table 1. Reaction of **5a** with Et₃N-nHF or aq. HF

$$\text{C}_{10}\text{H}_{21}-\text{C}\equiv\text{C}-\text{I}(\text{Ph})\text{BF}_4 \xrightarrow[\text{Solvent}]{\text{HF source}} \text{C}_{10}\text{H}_{21}-\text{C}(\text{F})=\text{C}-\text{I}(\text{Ph})\text{BF}_4$$

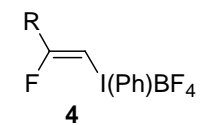
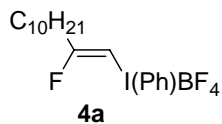
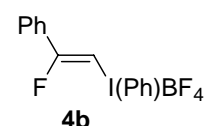
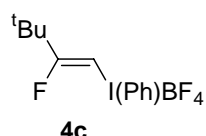
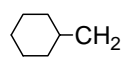
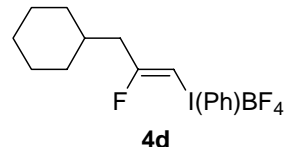
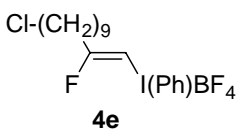
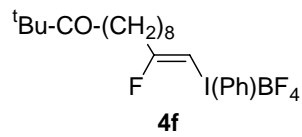
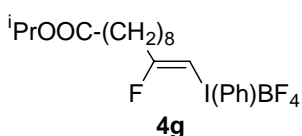
5a **4a**

Entry	HF source	Solvent	Temp.	Time / h	Yield ^{a)} / %
1	Et ₃ N-5HF	CH ₂ Cl ₂	r.t.	24	0
2	Et ₃ N-3HF	CH ₂ Cl ₂	r.t.	96	71
3	Et ₃ N-2HF	CH ₂ Cl ₂	r.t.	44	32 ^{b)}
4	Et ₃ N-3HF	---	r.t.	78	71
5	Et ₃ N-3HF	---	40 °C	8	72
6	Et ₃ N-3HF	---	60 °C	0.75	67
7	46% aq. HF	CHCl ₃	60 °C	84	81
8	30% aq. HF	CHCl ₃	60 °C	8	82
9	20% aq. HF	CHCl ₃	60 °C	6	84
10	10% aq. HF	CHCl ₃	60 °C	5	71

^a Isolated yield based on **5a** used. ^b 1,2,2-Trifluorododecane (**12**) was obtained in 26% yield.

Under the same reaction conditions, various (*Z*)-fluoroalkenyliodonium salts (**4a-g**) were stereoselectively synthesized in good yields from the corresponding alk-1-ynyl(phenyl)iodonium salts (**5**) having a normal alkyl or a sterically hindered group (Table 2). The introduction of various functional groups such as a chlorine, ketone or ester was also possible (Entries 5-7).

Table 2. Stereoselective syntheses of (*Z*)-2-fluoroalk-1-enyl(phenyl)iodonium tetrafluoroborates (**4**)

$R-C\equiv C-I(Ph)BF_4$	$\xrightarrow[CHCl_3, 60\text{ }^\circ C]{20\% \text{ aq. HF}}$			
5		4		
Entry	R	Time / h	Yield / % ^a	Product
1	C ₁₀ H ₂₁	6	84	
2	Ph	8	43	
3	^t Bu	12	84	
4		12	74	
5	Cl-(CH ₂) ₉	6	80	
6	^t Bu-CO-(CH ₂) ₈	6	72	
7	ⁱ PrOOC-(CH ₂) ₈	6	76	

^a Isolated yield

Pd-catalyzed cross-coupling reactions using (*Z*)-2-fluoroalk-1-enyliodonium salts (**4**)

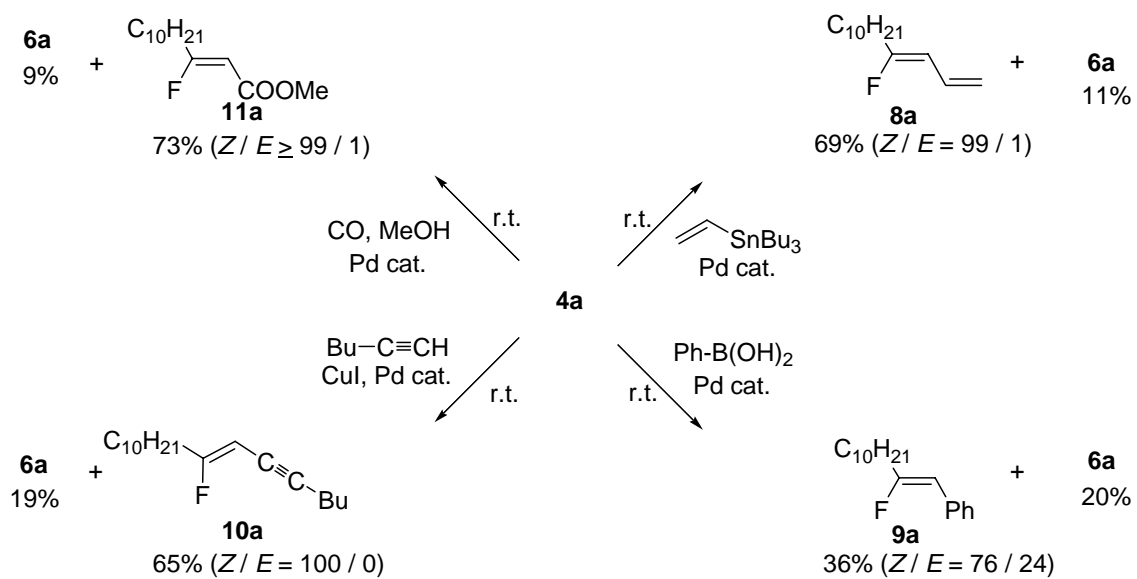
To obtain (*Z*)-2-fluoroalk-1-ene derivatives stereoselectively, various Pd-catalyzed cross-coupling reactions of the (*Z*)-fluoroalkenyliodonium salts (**4**) were examined. Initially, the Heck reaction of (*Z*)-2-fluorododec-1-enyl(phenyl)iodonium salt (**4a**) with methyl vinyl ketone was carried out in the presence of Pd(OAc)₂ and NaHCO₃ in DMF (Table 1, Entry 1) (refer to Chapter 3).^{5c,d,10} The coupling reaction smoothly proceeded at room temperature to give the desired product, (3*E*,5*Z*)-6-fluorohexadeca-3,5-dien-2-one (**7a**), in 79% yield [(3*E*,5*Z*) / (3*E*,5*E*) = 69 / 31]; however 4-phenyl-3-buten-2-one (**13**) (6%) and (*Z*)-2-fluoro-1-iodododec-1-ene (**6a**) (6%) were also generated. In order to suppress the formation of **13** and **6a**, various reaction conditions were examined. Although the stereoselectivity could be improved to [(3*E*,5*Z*) / (3*E*,5*E*) = 96 / 4] by carrying out the coupling reaction of **4a** using Pd(OAc)₂, KI and aq. NaHCO₃ at -20 °C (Entry 9), the formation of **13** and **6a** was always observed. The formation of these compounds is explained as follows: the reaction of the Pd catalyst to the phenyl-I bond of **4a** afforded a phenylpalladium intermediate, which would react with methyl vinyl ketone to give **13**, along with the generation of **6a** (refer to Chapter 2).^{5b,e} In the Heck reaction using (*E*)-2-fluorododec-1-enyliodonium salt, the coupling reaction preferentially took place at the alkenyl part and the formation of **13** was not observed (refer to Chapter 3).^{5c,d} Therefore, in the coupling reaction of **4a**, the fluorine atom at the *cis*-position to the iodonium group retarded the reaction of the Pd catalyst to the alkenyl-I bond and the formation of **13** and **6a** was promoted.

Table 3. Heck reaction of **4a**

Entry	Pd cat. (mol%)	Base (eq.)	Time / h	Yield ^a / %			7a (3E,5Z) / (3E,5E)
				7a	13	6a	
1	Pd(OAc) ₂ (5)	NaHCO ₃ (3.0)	1.5	79	6	6	69 / 31
2	PdI ₂ (5)	NaHCO ₃ (3.0)	2.0	78	7	8	87 / 13
3	Pd(OAc) ₂ (5), KI (10)	NaHCO ₃ (3.0)	1.5	75	7	7	86 / 14
4	Pd(OAc) ₂ (5), KI (5)	NaHCO ₃ (3.0)	1.0	75	6	7	89 / 11
5	Pd(OAc) ₂ (5), KI (5)	1.2M-NaHCO ₃ (1.2)	0.5	67	12	10	93 / 7
6 ^b	Pd(OAc) ₂ (5), KI (5)	1.2M-NaHCO ₃ (1.2)	12	70	9	8	96 / 4

^a Isolated yield ^bThe reaction was carried out at -20°C.

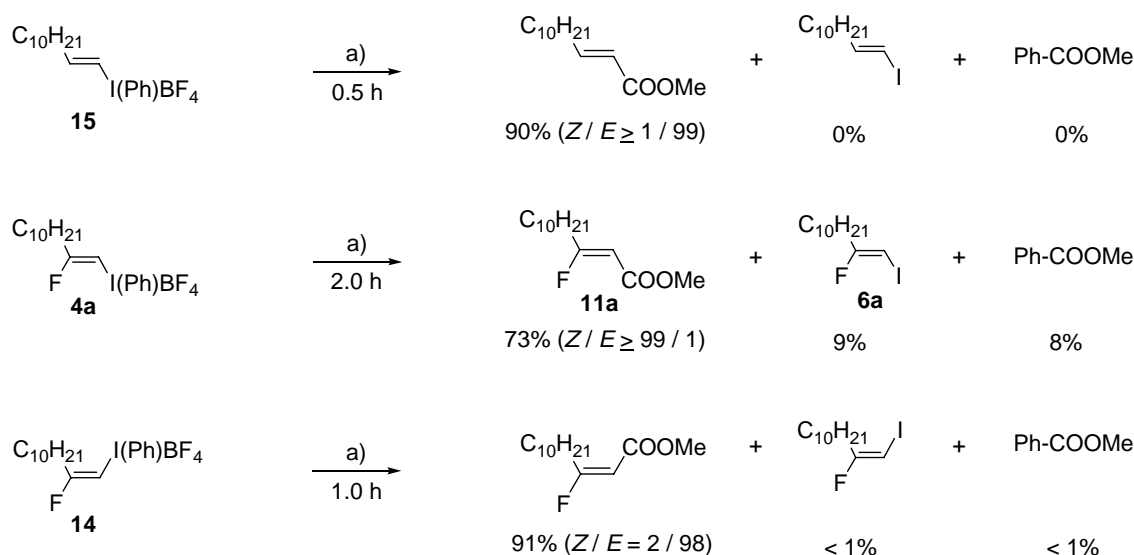
Pd-catalyzed cross-coupling reactions of **4a** with organostannanes (**8a**, Stille reaction),^{5d,11} organoboranes (**9a**, Suzuki-Miyaura reaction),^{5e,12} terminal alkynes (**10a**, Sonogashira reaction)^{3k,5f,13} or CO and methanol (**11a**, methoxycarbonylation)^{5b,14} also smoothly proceeded to give a variety of (*Z*)-2-fluoroalk-1-ene derivatives; however, the formation of **6a** was always observed (Scheme 4).



Scheme 4.

Effects of the vinylic fluorine atom on the Pd-catalyzed coupling reactions

To understand the formation of **6a** from the Pd-catalyzed coupling reactions using **4a**, methoxycarbonylation using **4a**, (*E*)-2-fluorododec-1-enyl(phenyl)iodonium salt (**14**) and (*E*)-dodec-1-enyl(phenyl)iodonium salt (**15**) was carried out under same reaction conditions (Scheme 5).



Conditions: a) CO 1 atm, MeOH, NaHCO₃ 1 eq., PdCl₂ 2 mol%, r.t.

Scheme 5.

As expected, the coupling reaction of unfluorinated alkenyliodonium salt (**15**) selectively took place at the alkenyl part to give α,β -unsaturated ester in 90% yield without the formation of methyl benzoate and iodododecene.¹⁴ The methoxycarbonylation of (*Z*)-fluoroalkenyliodonium salt (**4a**) proceeded slower than that of **15** to give (*Z*)- β -fluoro- α,β -unsaturated ester (**9a**) (73%) together with fluoriodoalkene (**6a**) (9%) and methyl benzoate (8%). Consequently, it was found that the existence of the fluorine atom affected the regioselectivity of the coupling reaction. The influence of the fluorine atom was investigated by the ¹H NMR of **4a** and **15** (Figure 1).

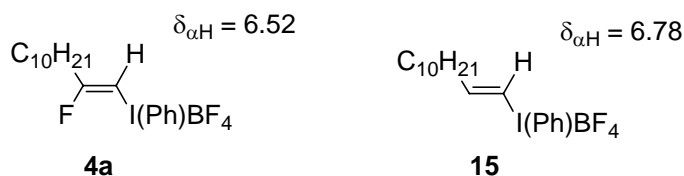


Figure 1.

When a fluorine atom was introduced to the *cis*-position of the iodonium group of unfluorinated alkenyliodonium salt (**15**), the α -hydrogen signal was shifted from 6.78 ppm to 6.52 ppm. It indicated the fluorine atom did not behave as an electron-withdrawing group but an electron-donating group (+I π effect).¹⁵ Therefore, the fluorine atom disturbed the oxidative addition of the Pd catalyst to the alkenyl-I bond, and the addition to the phenyl-I bond competitively proceeded.

Since the methoxycarbonylation of (*E*)-fluoroalkenyliodonium salt (**14**) afforded only a trace amount of (*E*)-2-fluoro-1-iodododec-1-ene (<1%) and methyl benzoate (<1%) as by-products, the coupling reaction of the fluoroalkenyliodonium salts was strongly affected by the fluorine atom at the *cis*-position of the iodonium group.

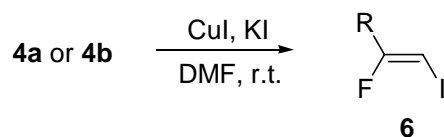
Stereoselective synthesis of (*Z*)-2-fluoro-1-iodoalk-1-enes (**6**)

In the Pd-catalyzed coupling reactions using (*Z*)-2-fluorododecenyliodonium salt (**4a**), the formation of (*Z*)-2-fluoro-1-iodododec-1-ene (**6a**) could not be suppressed. Consequently, compound **4a** was converted to **6a** beforehand, and **6a** was subjected to the Pd-catalyzed coupling reactions.

As described in Chapter 1, the transformation of **4a** to **6a** was carried out using CuI and KI in DMF (Table 4).^{5a,6a,14b} The iodination reaction of **4a** smoothly proceeded with 1eq. of CuI and KI to give **6a** in 87% yield after 12 h (Entry 1). The amount of CuI could be reduced to 5 mol% to **4a** (Entry 2), although the reaction did not proceed in the absence of it (Entry 3).^{14b} Under the same reaction conditions, (*Z*)-2-fluoro-2-phenyleth-1-enyl(phenyl)iodonium tetrafluoroborate (**4b**) was also

converted to (*Z*)-2-fluoro-1-iodo-2-phenylethene (**6b**) in 87% yield (Entry 4).

Table 4. Synthesis of (*Z*)-2-fluoro-1-iodoalk-1-ene (**6**)



Entry	CuI / eq.	KI / eq.	Time / h	Yield ^a / %	
1 (4a)	1.0	1.0	12	87	$\begin{array}{c} \text{C}_{10}\text{H}_{21} \\ \\ \text{C}=\text{C} \\ \quad \\ \text{F} \quad \text{I} \end{array}$ 6a
2 (4a)	0.05	1.0	36	89	6a
3 (4a)	0	1.5	24	0 ^b	---
4 (4b)	0.05	1.0	3	87	$\begin{array}{c} \text{Ph} \\ \\ \text{C}=\text{C} \\ \quad \\ \text{F} \quad \text{I} \end{array}$ 6b

^a Isolated yield based on **4** used. ^b Substrate was recovered unchanged.

Pd-catalyzed cross-coupling reactions using (*Z*)-2-fluoro-1-iodoalk-1-enes (**6**)

Pd-catalyzed cross-coupling reactions using **6a** and **6b** were carried out to obtain a variety of (*Z*)-2-fluoroalk-1-ene derivatives. Initially, the Heck reaction using fluoriodododecene (**6a**) with methyl vinyl ketone was examined (Table 5).

Table 5. Heck reaction of **6**

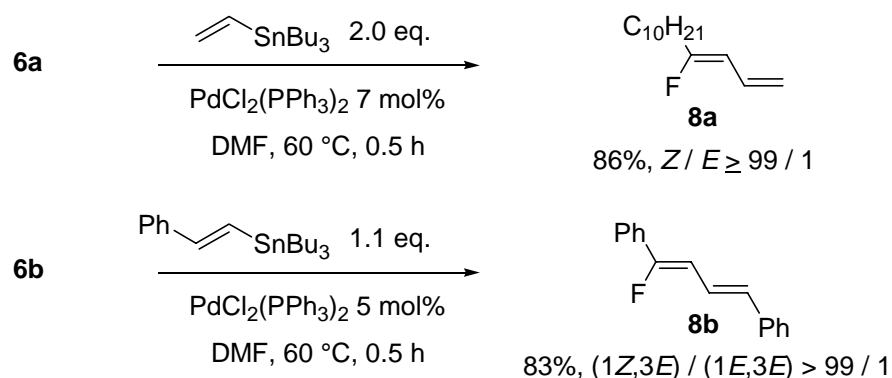
Entry	Pd cat. / mol%	Time / h	7		Product
			(3 <i>E</i> , 5 <i>Z</i>) / (3 <i>E</i> , 5 <i>E</i>)	Yield ^{a)} / %	
1 (6a)	Pd(OAc) ₂ (5), PPh ₃ (10)	2.5	96 / 4	71	
2 (6a)	PdCl ₂ (PPh ₃) ₂ (5)	6.0	96 / 4	70	7a
3 (6a)	Pd(PPh ₃) ₄ (5)	6.0	97 / 3	68	7a
4 (6a)	Pd(PPh ₃) ₄ (10)	4.0	98 / 2	77	7a
5 (6b)	Pd(PPh ₃) ₄ (10)	12	96 / 4	76	

a) Isolated yield based on **6**.

The coupling reaction using Pd(OAc)₂-PPh₃ or PdCl₂(PPh₃)₂, a common catalyst in the Heck reaction, smoothly proceeded at 60 °C with Et₃N in DMF to give the desired product, (3*E*,5*Z*)-6-fluorohexadeca-3,5-dien-2-one (**7a**), in 70-71% yield [(3*E*,5*Z*) / (3*E*,5*E*) = 96 / 4] (Table 5, Entries 1 and 2).^{10b,c} When the coupling reaction was carried out using 10 mol% of Pd(PPh₃)₄, **7a** was obtained in 77% yield with high stereoselectivity [(3*E*,5*Z*) / (3*E*,5*E*) = 98 / 2] and it was the best result (Entry 4). Under the reaction conditions, (*Z*)-2-fluoro-1-iodo-2-phenyleth-1-ene (**6b**) was also converted to (3*E*,5*Z*)-6-fluoro-6-phenylhexa-3,5-dien-2-one (**7b**) in 76% yield [(3*E*,5*Z*) / (3*E*,5*E*) = 96 / 4] (Entry 5).

The Stille coupling of **6a** with tributylvinylstannane was carried out at 60 °C in the presence of PdCl₂(PPh₃)₂, a common catalyst in the Stille reaction, in DMF to give (*Z*)-4-fluorotetradeca-1,3-diene (**8a**) in good yields with excellent stereoselectivity (*Z* / *E* ≥ 99 / 1) (Scheme 6).^{11d} Under the same reaction conditions, the coupling reaction between **6b** and

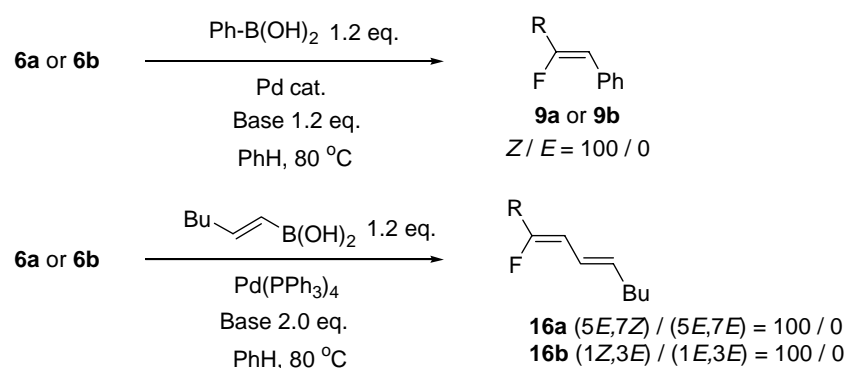
tributylstyrylstannane also gave (1*Z*,3*E*)-1-fluoro-1,4-diphenylbuta-1,3-diene (**8b**) in 83% yield [(1*Z*,3*E*) / (1*E*,3*E*) ≥ 99 / 1].

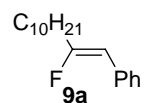
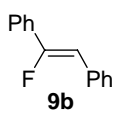

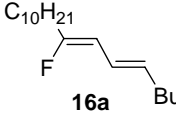


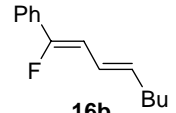


Scheme 6. Stille reaction of **6**

The Suzuki-Miyaura reaction using **6a** with phenylboronic acid smoothly proceeded at 80 °C in the presence of PdCl₂(PPh₃)₂ and K₂CO₃ in benzene to give (*Z*)-2-fluoro-1-phenyldodec-1-ene (**7a**) in 88% yield with excellent stereoselectivity (*Z* / *E* = 100 / 0) (Table 6, Entry 1) (refer to Chapter 4).^{12c} Under the same reaction conditions, **6b** was also converted to (*Z*)-1-fluoro-1,2-diphenylethene (**7b**) in 85% yield (Entry 4). The coupling reaction of **6a** with (*E*)-hex-1-enylboronic acid using Pd(PPh₃)₄ and an aqueous solution of KOH completed in 8 h to give (5*E*,5*Z*)-8-fluorooctadeca-5,7-diene (**16a**) in 81% yield [(5*E*,7*Z*) / (5*E*,7*E*) = 100 / 0] (Entry 5). As for the base, an ethanol solution of KOH was found to be more effective than the aqueous solution of it, and **16a** was obtained in 83% yield in 1 h (Entry 6). Under the same reaction conditions, **6b** was also transformed to (1*Z*,3*E*)-1-fluoro-1-phenylocta-1,3-diene (**16b**) in 72% yield in 0.5 h (Entry 7).

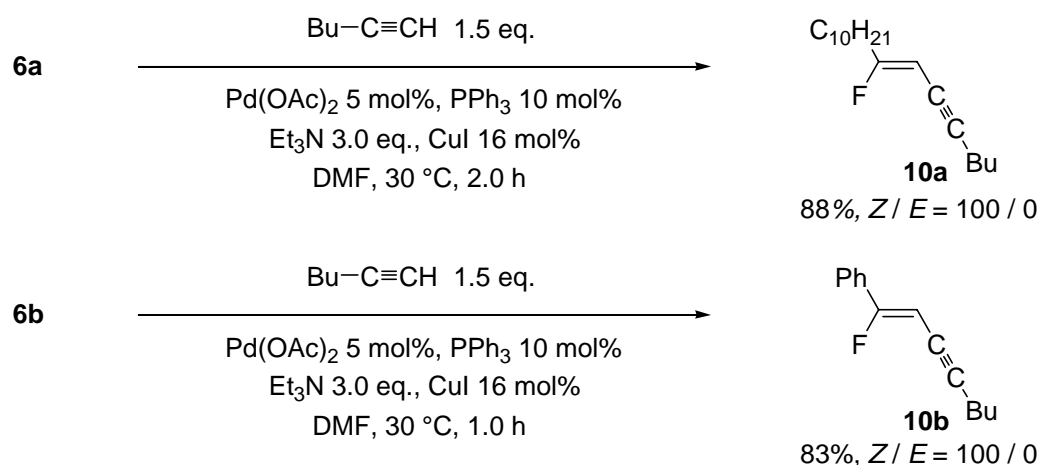
Table 6. Suzuki-Miyaura reaction of **6**



Entry	R'-B(OH) ₂	Pd cat. / 5 mol%	Base	Time / h	Yield ^a / %	Product
1 (6a)	Ph	PdCl ₂ (PPh ₃) ₂	2M-K ₂ CO ₃	1.5	88	
2 (6a)	Ph	PdBnCl(PPh ₃) ₂	2M-K ₂ CO ₃	1.5	86	9a
3 (6a)	Ph	Pd(PPh ₃) ₄	2M-K ₂ CO ₃	10.0	76	9a
4 (6b)	Ph	PdCl ₂ (PPh ₃) ₂	2M-K ₂ CO ₃	2.0	85	
5 (6a)		Pd(PPh ₃) ₄	2M-KOH	8.0	81	
6 (6a)		Pd(PPh ₃) ₄	2M-KOH-EtOH	1.0	83	16a
7 (6b)		Pd(PPh ₃) ₄	2M-KOH-EtOH	0.5	72	

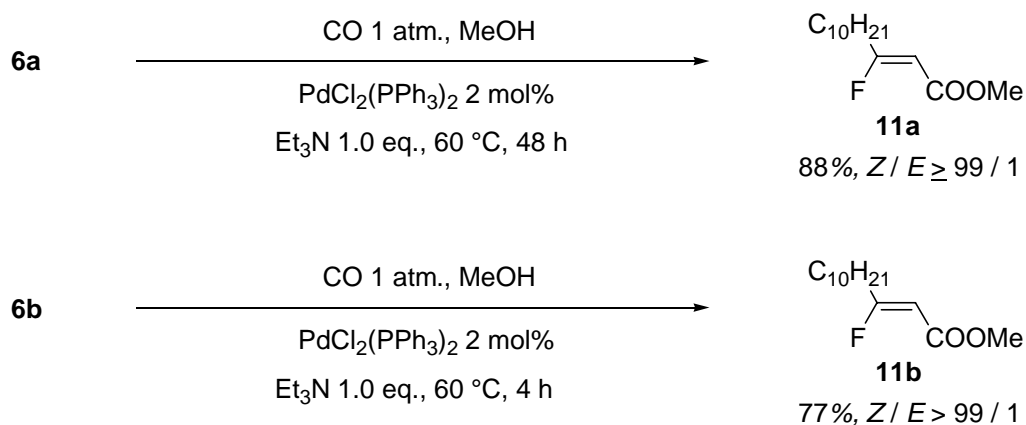
^a Isolated yield based on **6**.

The Sonogashira reaction of **6a** and **6b** with hex-1-yne was also carried out using Pd(OAc)₂, PPh₃, CuI and Et₃N at 30 °C (Scheme 7) (refer to Chapter 6).^{13c} The coupling reactions smoothly proceeded to give (*Z*)-8-fluorooctadeca-7-en-5-yne (**8a**) and (*Z*)-1-fluoro-1-phenylocta-1-en-3-yne (**8b**) in good yields with excellent stereoselectivity (*Z*/*E* = 100/0).



Scheme 7. Sonogashira reaction of **6**

The Pd-catalyzed methoxycarbonylation of **6** was carried out in MeOH under 1 atm of CO (Scheme 8).^{14d} The reaction of **6a** and **6b** smoothly proceeded at 60 °C in the presence of PdCl₂(PPh₃)₂, a common catalyst in the alkoxy carbonylation, and Et₃N to give methyl (*Z*)-3-fluorotridec-2-enoate (**9a**) (88%) and (*Z*)-3-fluoro-3-phenylprop-2-enoate (**9b**) (77%), respectively, with excellent stereoselectivity (*Z* / *E* ≥ 99 / 1).



Scheme 8. Pd-catalyzed methoxycarbonylation of **6**

Conclusion

(*Z*)-2-Fluoroalk-1-enyl(phenyl)iodonium salts were stereoselectively synthesized in good yields by an HF addition to alkynyl(phenyl)iodonium salts with hydrofluoric acid. The fluoroalkenylidonium salts were readily converted to (*Z*)-2-fluoro-1-iodoalk-1-enes with CuI and KI, and they were subjected to Pd-catalyzed coupling reactions with α,β -unsaturated carbonyl compounds (Heck reaction), CO and methanol (methoxycarbonylation), organostannanes (Stille reaction), organoboranes (Suzuki-Miyaura reaction) or terminal alkynes (Sonogashira reaction). Finally, a variety of (*Z*)-2-fluoroalk-1-ene derivatives were stereoselectively obtained in good yields.

Experimental

General.

The IR spectra were recorded using a JASCO FT/IR-410. The ^1H -NMR (400 MHz), ^{19}F -NMR (376 MHz) and ^{13}C -NMR (100 MHz) spectra were recorded in CDCl_3 on a JEOL JNM-A400II FT NMR and the chemical shifts, δ , are referred to TMS (^1H , ^{13}C) and CFCl_3 (^{19}F). The low- and high-resolution mass spectra were measured on a JEOL JMS-700TZ, JMS-FAB mate or JMS-HX110. The elemental microanalyses were done using a Yanagimoto CHN Corder MT-5. Silica gel 60 N of Kanto Chemical Co., Inc. for column chromatography and Merck silica gel 5715 for analytical thin layer chromatography were used. $\text{Et}_3\text{N}\cdot 2\text{HF}$ was prepared as CH_2Cl_2 solution by the addition of Et_3N to $\text{Et}_3\text{N}\cdot 3\text{HF}$ ¹⁶ in CH_2Cl_2 before use. Commercial CHCl_3 was distilled before use to remove EtOH added as a stabilizer. Hydrofluoric acid (46%) was purchased from Wako Chemical Co., Inc. and diluted with water to make the hydrofluoric acid of other concentrations. $\text{Pd}(\text{PPh}_3)_4$,^{17a} $\text{BnPdCl}(\text{PPh}_3)_2$,^{17b} 3,3-dimethylbut-1-yne¹⁸ and (*E*)-dodec-1-enyl(phenyl)iodonium tetrafluoroborate^{14b} were prepared according to the literatures. Phenylboronic acid, phenylacetylene, hex-1-yne, methyl vinyl ketone, PdCl_2 , $\text{Pd}(\text{OAc})_2$, $\text{PdCl}_2(\text{PPh}_3)_2$, and PPh_3 purchased from Tokyo Kasei Co., Ltd., and PdI_2 purchased from Aldrich Chemical Company, Inc. were used without further purification. Preparation of $\text{Et}_3\text{N}\cdot 5\text{HF}$, dodec-1-yne, 3-cyclohexylprop-1-yne, 11-chloroundec-1-yne, methyl undec-10-ynoate and 2,2-dimethyltridec-12-yn-3-one were shown in Chapter 1. Preparation of tributylvinylstannane and tributylstyrylstannane were shown in Chapter 3. Preparation of (*E*)-hex-1-enylboronic acid was shown in Chapter 4. The procedures for the preparation of alk-1-ynyl(phenyl)iodonium tetrafluoroborates (**5**) was shown in Chapter 7.^{19a,b}

For the spectrum information of **5a-f**, see Chapter 7.

Preparation of (*Z*)-2-fluoroalk-1-enyl(phenyl)iodonium tetrafluoroborate (4**) by the reaction of **5** with Et₃N-3HF**

Typical Procedure: In a Teflon™ PFA vessel were placed dodec-1-ynyl(phenyl)iodonium tetrafluoroborate (**5a**)^{19a} (228 mg, 0.5 mmol) and Et₃N-3HF (805 mg, 5 mmol) at room temperature, and the mixture was stirred at 40 °C for 8 h. The reaction mixture was poured into water (100 mL) and extracted with CH₂Cl₂ (10 mL) four times. The combined organic phase was dried over MgSO₄ and concentrated under reduced pressure. The resulting viscous oil was dissolved in CH₂Cl₂ (1 mL) and a white suspension was formed by the addition of hexane (40 mL). The white suspension was left in a refrigerator for 2 h and clear upper liquid was removed by decantation. The remained white solid was washed with hexane (5 mL) again, separated by decantation, and dried in vacuo to give (*Z*)-2-fluorododec-1-enyl(phenyl)iodonium tetrafluoroborate (**4a**) (72%, 171 mg, 0.36 mmol).

Preparation of **4 by the reaction of **5** with hydrofluoric acid**

Typical procedure: In a Teflon™ PFA vessel were placed **5a** (228 mg, 0.5 mmol), CHCl₃ (2 mL) and a 20% hydrofluoric acid (500 mg, 5 mmol) at room temperature, and the mixture was vigorously stirred at 60 °C for 6 h. The reaction mixture was poured into a 0.5 M aq. NaBF₄ (20 mL) and extracted with CH₂Cl₂ (10 mL) four times. The combined organic phase was dried over MgSO₄ and concentrated under reduced pressure. The resulting viscous oil was dissolved in CH₂Cl₂ (1 mL) and a white suspension was formed by the addition of hexane (40 mL). The white suspension was left in a refrigerator for 2 h and clear upper liquid was removed by decantation. The remained precipitate was washed with hexane (40 mL) again, separated from hexane by decantation, and dried in vacuo to give pure **4a** (84%, 200 mg, 0.42 mmol).

(Z)-2-Fluorododec-1-enyl(phenyl)iodonium tetrafluoroborate (4a).

M.p. 27–28 °C, $\delta_{\text{H}}(\text{CDCl}_3)$ 0.88 (3H, t, J 7.3 Hz, 12-H), 1.19-1.31 (14H, m), 1.52-1.60 (2H, m, 4-H), 2.57 (2H, dt, $^3J_{\text{H-F}}$ 17.3, J 7.6 Hz, 3-H), 6.52 [1H, d, $^3J_{\text{H-F(olefin)}}$ 33.2 Hz, 1-H], 7.45-8.02 (5H, m, Ph); $\delta_{\text{F}}(\text{CDCl}_3)$ -63.90 [1F, dt, $^3J_{\text{H-F}}$ 17.3, $^3J_{\text{H-F(olefin)}}$ 33.2 Hz, 2-F]; $\delta_{\text{C}}(\text{CDCl}_3)$ 14.11, 22.67, 25.48, 28.69, 29.03, 29.26, 29.35, 29.47, 31.86, 32.26 (d, $^2J_{\text{C-F}}$ 23.2 Hz, 3-C), 74.20 (d, $^2J_{\text{C-F}}$ 21.5 Hz, 1-C), 111.4, 132.28 (2C), 132.64, 135.27 (2C), 174.19 (d, $^1J_{\text{C-F}}$ 280.0 Hz, 2-C); $\nu(\text{KBr})/\text{cm}^{-1}$ 3061, 3048, 2956, 2923, 2852, 1653, 1564, 1470, 1440, 1301, 1115, 1055, 989, 880, 738, 680; [HR FAB-MS: Calc. for $\text{C}_{18}\text{H}_{27}\text{FI} (\text{M} - \text{BF}_4)$: 389.1142. Found: $\text{M}^+ - \text{BF}_4$, 389.1127]. Found: C, 45.48; H, 5.85%. Calcd for $\text{C}_{18}\text{H}_{27}\text{BF}_5\text{I}$: C, 45.41; H, 5.72%.

(Z)-2-Fluoro-2-phenyleth-1-enyl(phenyl)iodonium tetrafluoroborate (4b).

M.p. 136.5–137.0 °C, $\delta_{\text{H}}(\text{DMSO-}d_7)$ 7.53-7.77 (8H, m), 7.94 [1H, d, $^3J_{\text{H-F(olefin)}}$ 37.5 Hz, 1-H], 8.17 (2H, d, J 8.03 Hz); $\delta_{\text{F}}(\text{DMSO-}d_7)$ -83.80 [1F, d, $^3J_{\text{H-F(olefin)}}$ 37.5 Hz, 2-F]; $\delta_{\text{C}}(\text{DMSO-}d_7)$ 80.43 (d, $^2J_{\text{C-F}}$ 21.5 Hz, 1-C), 115.44, 125.94 (2C, d, $^3J_{\text{C-F}}$ 7.4 Hz, ortho), 127.36 (d, $^2J_{\text{C-F}}$ 28.0 Hz, ipso), 129.30 (2C), 131.84 (2C), 132.03, 132.47, 135.04 (2C), 164.57 (d, $^1J_{\text{C-F}}$ 261.8 Hz, 2-C); $\nu(\text{KBr})/\text{cm}^{-1}$ 3113, 1625, 1575, 1496, 1470, 1445, 1290, 1084, 1037, 987, 796, 768, 740, 677, 651, 634, 603, 521; [HR FAB-MS: Calc. for $\text{C}_{14}\text{H}_{11}\text{FI} (\text{M} - \text{BF}_4)$: 324.9890. Found: $\text{M}^+ - \text{BF}_4$, 324.9868]. Found: C, 40.63; H, 2.67%. Calcd for $\text{C}_{14}\text{H}_{11}\text{BF}_5\text{I}$: C, 40.82; H, 2.69%.

(Z)-3,3-Dimethyl-2-fluorobut-1-enyl(phenyl)iodonium tetrafluoroborate (4c).

M.p. 160.7-161.5 °C, $\delta_{\text{H}}(\text{CDCl}_3)$ 1.24 (9H, s, ^tBu), 6.55 [1H, d, $^3J_{\text{H-F(olefin)}}$ 33.9 Hz, 1-H], 7.52-8.01 (5H, m, Ph); $\delta_{\text{F}}(\text{CDCl}_3)$ -70.65 [1F, d, $^3J_{\text{H-F(olefin)}}$ 33.9 Hz, 2-F]; $\delta_{\text{C}}(\text{DMSO-}d_7)$ 26.39 (3C), 36.39 (d, $^2J_{\text{C-F}}$ 22.3 Hz, 3-C), 79.39 (d, $^2J_{\text{C-F}}$ 21.5 Hz, 1-C), 115.05, 131.76 (2C), 131.88, 134.68 (2C), 176.45 (d, $^1J_{\text{C-F}}$ 275.9 Hz, 2-C); $\nu(\text{KBr})/\text{cm}^{-1}$ 3120, 3094, 2976, 2941, 2908, 2876, 1633, 1471, 1444, 1284, 1073, 1034, 988, 867, 764, 744, 679; [HR FAB-MS: Calc. for

$C_{12}H_{15}FI$ ($M - BF_4$): 305.0203. Found: $M^+ - BF_4$, 305.0223]. Found: C, 36.63; H, 3.76%. Calcd for $C_{12}H_{15}BF_5I$: C, 36.77; H, 3.86%.

(Z)-3-Cyclohexyl-2-fluoroprop-1-enyl(phenyl)iodonium tetrafluoroborate (4d).

M.p. 84.0-84.5 °C, $\delta_H(CDCl_3)$ 0.86-1.25 (5H, m), 1.60-1.69 (6H, m), 2.47 (2H, dd, $^3J_{H-F}$ 21.2, J 6.8 Hz, 3-H), 6.49 [1H, d, $^3J_{H-F(olefin)}$ 32.7 Hz, 1-H], 7.46-8.03 (5H, m, Ph); $\delta_F(CDCl_3)$ -63.00 [1F, dt, $^3J_{H-F}$ 21.2, $^3J_{H-F(olefin)}$ 32.7 Hz, 2-F]; $\delta_C(CDCl_3)$ 25.80 (2C), 25.87, 32.54 (2C), 35.25, 39.70 (d, $^2J_{C-F}$ 23.1 Hz, 3-C), 74.78 (d, $^2J_{C-F}$ 21.4 Hz, 1-C), 111.60, 132.25 (2C), 132.63, 135.30 (2C), 173.07 (d, $^1J_{C-F}$ 280.0 Hz, 2-C); $\nu(KBr)/cm^{-1}$ 3122, 3097, 3066, 2929, 2852, 1652, 1564, 1472, 1444, 1115, 1049, 873, 738, 678; [HR FAB-MS: Calc. for $C_{15}H_{19}FI$ ($M - BF_4$): 345.0516. Found: $M^+ - BF_4$, 345.0505]. Found: C, 41.74; H, 4.45%. Calcd for $C_{15}H_{19}BF_5I$: C, 41.70; H, 4.43%.

(Z)-11-Chloro-2-fluoroundec-1-enyl(phenyl)iodonium tetrafluoroborate (4e).

M.p. 34.5-35.0 °C, $\delta_H(CDCl_3)$ 1.21-1.44 (10H, m) 1.53-1.61 (2H, m, 4-H), 1.72-1.79 (2H, m, 10-H), 2.58 (2H, dt, $^3J_{H-F}$ 17.3, J 7.3 Hz, 3-H), 3.53 (2H, t, J 6.6 Hz, 11-H), 6.52 [1H, d, $^3J_{H-F(olefin)}$ 33.2 Hz, 1-H], 7.46-8.03 (5H, m, Ph); $\delta_F(CDCl_3)$ -63.99 [1F, dt, $^3J_{H-F}$ 17.7, $^3J_{H-F(olefin)}$ 33.1 Hz, 2-F]; $\delta_C(CDCl_3)$ 25.32, 26.66, 28.46, 28.59, 28.78, 29.02, 32.04 (d, $^2J_{C-F}$ 23.1 Hz, 3-C), 32.45, 45.11, 74.22 (d, $^2J_{C-F}$ 21.5 Hz, 1-C), 111.42, 132.16 (2C), 132.50, 135.13 (2C), 173.90 (d, $^1J_{C-F}$ 279.1 Hz, 2-C); $\nu(KBr)/cm^{-1}$ 3060, 2930, 2853, 1650, 1564, 1469, 1441, 1306, 1106, 1056, 989, 881, 740, 681, 654; [HR FAB-MS: Calc. for $C_{17}H_{24}ClFI$ ($M - BF_4$): 409.0595. Found: $M^+ - BF_4$, 409.0609]. Found: C, 40.94; H, 4.85%. Calcd for $C_{17}H_{24}BClF_5I$: C, 41.12; H, 4.87%.

(Z)-12,12-Dimethyl-2-fluoro-11-oxotridec-1-enyl(phenyl)iodonium tetrafluoroborate (4f).

Oil, $\delta_H(CDCl_3)$ 1.26 (9H, s, tBu), 1.17-1.34 (8H, m), 1.50-1.57 (4H, m), 2.46

(2H, t, J 6.8 Hz, 10-H), 2.59 (2H, dt, $^3J_{\text{H-F}}$ 17.1, J 7.8 Hz, 3-H), 6.50 [1H, d, $^3J_{\text{H-F(olefin)}}$ 32.9 Hz, 1-H], 7.47-8.03 (5H, m, Ph); $\delta_{\text{F}}(\text{CDCl}_3)$ -63.77 [1F, dt, $^3J_{\text{H-F}}$ 17.1, $^3J_{\text{H-F(olefin)}}$ 32.9 Hz, 2-F]; $\delta_{\text{C}}(\text{CDCl}_3)$ 23.80, 25.41, 26.41 (3C), 28.52, 28.80, 29.09, 29.17, 32.21 (d, $^2J_{\text{C-F}}$ 23.1 Hz, 3-C), 36.37, 44.11, 74.30 (d, $^2J_{\text{C-F}}$ 21.5 Hz, 1-C), 111.42, 132.31 (2C), 132.68, 135.28 (2C), 174.11 (d, $^1J_{\text{C-F}}$ 280.0 Hz, 2-C), 216.29; $\nu(\text{neat})/\text{cm}^{-1}$ 3104, 2932, 2858, 1702, 1646, 1565, 1472, 1444, 1366, 1065, 988, 741, 679, 651; [HR FAB-MS: Calc. for $\text{C}_{21}\text{H}_{31}\text{FIO}$ ($M - \text{BF}_4$): 445.1404. Found: $M^+ - \text{BF}_4$, 445.1415]. Found: C, 47.62; H, 5.91%. Calcd for $\text{C}_{21}\text{H}_{31}\text{BF}_5\text{IO}$: C, 47.39; H, 5.87%.

(*Z*)-10-Isopropoxycarbonyl-2-fluorodec-1-enyl(phenyl)iodonium tetrafluoroborate (4g).

Oil, $\delta_{\text{H}}(\text{CDCl}_3)$ 1.20-1.32 (14H, m), 1.53-1.62 (4H, m), 2.24 (2H, t, J 7.3 Hz, 10-H), 2.58 (2H, dt, $^3J_{\text{H-F}}$ 17.3, J 7.6 Hz, 3-H), 4.96-5.03 (1H, m, Me_2CH), 6.51 [1H, d, $^3J_{\text{H-F(olefin)}}$ 32.9 Hz, 1-H], 7.47-8.03 (5H, m, Ph); $\delta_{\text{F}}(\text{CDCl}_3)$ -63.89 [1F, dt, $^3J_{\text{H-F}}$ 16.9, $^3J_{\text{H-F(olefin)}}$ 33.1 Hz, 2-F]; $\delta_{\text{C}}(\text{CDCl}_3)$ 21.67 (2C), 24.74, 25.25, 28.36, 28.63, 28.73, 28.7, 31.93 (d, $^2J_{\text{C-F}}$ 23.1 Hz, 3-C), 34.46, 67.26, 74.21 (d, $^2J_{\text{C-F}}$ 21.5 Hz, 1-C), 111.46, 132.09 (2C), 132.43, 135.03 (2C), 173.27, 173.78 (d, $^1J_{\text{C-F}}$ 279.2 Hz, 2-C); $\nu(\text{neat})/\text{cm}^{-1}$ 3104, 2980, 2933, 2857, 1727, 1646, 1565, 1470, 1445, 1374, 1109, 1064, 988, 741, 679, 651; [HR FAB-MS: Calc. for $\text{C}_{20}\text{H}_{29}\text{FIO}_2$ ($M - \text{BF}_4$): 447.1196. Found: $M^+ - \text{BF}_4$, 447.1225]. Found: C, 44.89; H, 5.57%. Calcd for $\text{C}_{20}\text{H}_{29}\text{BF}_5\text{IO}_2$: C, 44.97; H, 5.47%.

10-Isopropoxycarbonyldec-1-ynyl(phenyl)iodonium tetrafluoroborate (5g).

Oil, $\delta_{\text{H}}(\text{CDCl}_3)$ 1.20-1.39 (14H, m), 1.56-1.61 (4H, m), 2.25 (2H, t, J 7.3 Hz, 10-H), 2.65 (2H, t, J 7.1 Hz, 3-H), 4.97-5.03 (1H, m, ^iPr), 7.54-8.07 (5H, m, Ph); $\delta_{\text{C}}(\text{CDCl}_3)$ 16.25, 20.46, 21.56 (2C), 24.63, 27.21, 28.29, 28.36, 28.61, 28.64, 34.38, 67.34, 113.14, 114.34, 132.41 (2C), 132.68, 133.78 (2C), 173.43; $\nu(\text{neat})/\text{cm}^{-1}$ 3090, 3062, 2980, 2932, 2857, 2182, 1726, 1691, 1469, 1445, 1375, 1182, 1107, 985, 741, 676; [HR FAB-MS: Calc. for $\text{C}_{20}\text{H}_{28}\text{IO}_2$ (M

- BF₄): 427.1134. Found: M⁺ - BF₄, 427.1134]. Found: C, 46.50; H, 5.43%. Calcd for C₂₀H₂₈BF₄IO₂: C, 46.72; H, 5.49%.

Syntheses of (*Z*)-2-fluoro-1-iodoalk-1-enes (**6**) from **4**

Typical procedure: To a DMF solution (4 mL) of **4a** (238 mg, 0.5 mmol) were added CuI (4.8 mg, 0.025 mmol) and KI (83 mg, 0.5 mmol), and the mixture was stirred at room temperature for 36 h. The reaction mixture was poured into 3 M aq. NH₄Cl (15 mL) and extracted with ether (10 mL) three times. The combined organic phase was dried over MgSO₄ and concentrated under reduced pressure. In order to remove a generated iodobenzene, the reaction mixture was kept at 40 °C and 0.01 mmHg for 1 h. (*Z*)-2-Fluoro-1-iodododec-1-ene (**6a**) was isolated by column chromatography (silica gel; hexane) in 89% yield (139 mg, *Z* isomer only).

(*Z*)-2-Fluoro-1-iodododec-1-ene (**6a**).

Oil, $\delta_{\text{H}}(\text{CDCl}_3)$ 0.88 (3H, t, J 7.1 Hz, 12-H), 1.20-1.37 (14H, m), 1.48-1.55 (2H, m, 4-H), 2.33 (2H, dt, $^3J_{\text{H-F}}$ 16.6, J 7.6 Hz, 3-H), 5.17 [1H, d, $^3J_{\text{H-F(olefin)}}$ 34.6 Hz, 1-H]; $\delta_{\text{F}}(\text{CDCl}_3)$ -79.84 [1F, dt, $^3J_{\text{H-F}}$ 16.6, $^3J_{\text{H-F(olefin)}}$ 34.6 Hz]; $\delta_{\text{C}}(\text{CDCl}_3)$ 14.13, 22.69, 25.91, 28.76, 29.22, 29.31, 29.46, 29.56, 31.89, 32.80 (d, $^2J_{\text{C-F}}$ 26.4 Hz, 3-C), 50.65 (d, $^2J_{\text{C-F}}$ 27.3 Hz, 1-C), 166.67 (d, $^1J_{\text{C-F}}$ 261.3 Hz, 2-C); $\nu(\text{neat})/\text{cm}^{-1}$ 2955, 2925, 2854, 1656, 1466, 1117, 876, 746; [HR EI-MS: Calc. for C₁₂H₂₂FI (*M*): 312.0750. Found: M⁺, 312.0732]. Found: C, 45.99; H, 6.88%. Calcd for C₁₂H₂₂FI: C, 46.16; H, 7.10%.

(*Z*)-2-Fluoro-1-iodo-2-phenylethene (**6b**).

Oil, $\delta_{\text{H}}(\text{CDCl}_3)$ 6.08 [1H, d, $^3J_{\text{H-F(olefin)}}$ 34.4 Hz, 1-H], 7.36-7.52 (5H, m, Ph); $\delta_{\text{F}}(\text{CDCl}_3)$ -90.62 [1F, d, $^3J_{\text{H-F(olefin)}}$ 34.4 Hz]; $\delta_{\text{C}}(\text{CDCl}_3)$ 53.40 (d, $^2J_{\text{C-F}}$ 28.8 Hz, 1-C), 124.64 (2C, d, $^3J_{\text{C-F}}$ 5.8 Hz, ortho), 128.67 (2C, d, $^4J_{\text{C-F}}$ 1.7 Hz, meta), 129.83, 130.86 (d, $^2J_{\text{C-F}}$ 28.9 Hz, ipso), 163.06 (d, $^1J_{\text{C-F}}$ 251.9 Hz, 2-C); $\nu(\text{neat})/\text{cm}^{-1}$ 3095, 3058, 1629, 1574, 1495, 1445, 1281, 1187, 1034, 1015, 791, 768, 741, 687, 606; [HR EI-MS: Calc. for C₈H₆FI (*M*): 247.9498.

Found: M⁺, 247.9480]. Found: C, 38.78; H, 2.48%. Calcd for C₈H₆FI: C, 38.74; H, 2.44%.

Synthesis of (3*E*,5*Z*)-6-fluorohexadeca-3,5-dien-2-one (**7a**) from **4a**

To a mixture of Pd(OAc)₂ (5.6 mg, 0.025 mmol) and KI (4.2 mg, 0.025 mmol) in DMF (1.5 mL) were added 1.2 M aq. NaHCO₃ (0.5 mL, 0.60 mmol) and methyl vinyl ketone (88 mg, 1.25 mmol) at room temperature. The reaction mixture was then cooled to -20 °C and a DMF solution (1 mL) of **4a** (238 mg, 0.5 mmol) was added. After stirring for 12 h at -20 °C, the reaction mixture was poured into 3 M aq. NH₄Cl (15 mL) and extracted with ether (10 mL) three times. The combined organic phase was dried over MgSO₄ and concentrated under reduced pressure. The product **7a** was isolated by column chromatography (silica gel; hexane-diethyl ether) in 70% yield [89 mg, (3*E*,5*Z*) / (3*E*,5*E*) = 96 / 4].

Synthesis of **7** from **6**

Typical Procedure: To a DMF solution (2.5 mL) of Pd(PPh₃)₄ (57.8 mg, 0.05 mmol) were added Et₃N (505 mg, 5 mmol), methyl vinyl ketone (88 mg, 1.25 mmol) and **6a** (156 mg, 0.5 mmol) at room temperature and the mixture was stirred at 60 °C for 4 h. The reaction mixture was poured into 3 M aq. NH₄Cl (15 mL) and extracted with ether (10 mL) three times. The combined organic phase was dried over MgSO₄ and concentrated under reduced pressure. The product **7a** was isolated by column chromatography (silica gel; hexane-diethyl ether) in 77% yield (98 mg, *Z* / *E* = 98 / 2).

(3*E*,5*Z*)-6-Fluorohexadeca-3,5-dien-2-one (**7a**).

Oil, δ_H(CDCl₃) 0.88 (3H, t, *J* 7.1 Hz, 16-H), 1.23-1.35 (14H, m), 1.54-1.57 (2H, m, 8-H), 2.25-2.33 (5H, m), 5.44 [1H, dd, *J* 11.2, ³*J*_{H-F(olefin)} 33.4 Hz, 5-H], 6.04 (1H, d, *J* 15.9 Hz, 3-H), 7.42 (1H, dd, *J* 11.2, 15.9 Hz, 4-H); δ_F(CDCl₃) -92.13 [1F, dt, ³*J*_{H-F} 17.7, ³*J*_{H-F(olefin)} 33.4 Hz]; δ_C(CDCl₃) 14.08,

22.64, 25.85, 26.71, 28.88, 29.22, 29.27, 29.42, 29.51, 31.85, 32.45 (d, $^2J_{C-F}$ 24.0 Hz, 7-C), 105.48 (d, $^2J_{C-F}$ 11.5 Hz, 5-C), 128.77 (d, $^4J_{C-F}$ 3.2 Hz, 3-C), 135.50 (d, $^3J_{C-F}$ 6.6 Hz, 4-C), 167.43 (d, $^1J_{H-F}$ 274.2 Hz, 6-C), 198.70; $\nu(\text{neat})/\text{cm}^{-1}$ 3057, 2951, 2926, 2855, 1695, 1659, 1599, 1466, 1361, 1254, 1134, 982, 866, 722; [HR FAB-MS: Calc. for $C_{16}H_{27}FO$ ($M - BF_4$): 254.2046. Found: $M^+ - BF_4$, 254.2037].

(3*E*,5*Z*)-6-Fluoro-6-phenylhexa-3,5-dien-2-one (7b).

M.p. 89.2-90.0 °C, $\delta_H(\text{CDCl}_3)$ 2.35 (3H, s, Me), 6.24 (1H, d, J 15.9 Hz, 3-H), 6.27 [1H, dd, J 11.2, $^3J_{H-F(\text{olefin})}$ 33.2 Hz, 5-H], 7.42-7.65 (6H, m); $\delta_F(\text{CDCl}_3)$ -108.44 [1F, d, $^3J_{H-F(\text{olefin})}$ 33.2 Hz]; $\delta_C(\text{CDCl}_3)$ 26.96, 104.76 (d, $^2J_{C-F}$ 13.3 Hz, 5-C), 124.88 (2C, d, $^3J_{C-F}$ 7.4 Hz, ortho), 128.78 (2C, d, $^4J_{C-F}$ 2.5 Hz, meta), 130.31 (d, $^3J_{C-F}$ 4.1 Hz, 3-C), 130.50, 130.74 (d, $^2J_{C-F}$ 26.4 Hz, ipso), 135.25 (d, $^3J_{C-F}$ 5.8 Hz, 4-C), 161.83 (d, $^1J_{C-F}$ 265.1 Hz, 6-C), 198.42; $\nu(\text{KBr})/\text{cm}^{-1}$ 1658, 1631, 1363, 1292, 1257, 1008, 976, 768, 692; [HR FAB-MS: Calc. for $C_{12}H_{11}FO$ (M): 190.0794. Found: M^+ , 190.0808]. Found: C, 75.75; H, 5.93%. Calcd for $C_{12}H_{11}FO$: C, 75.77; H, 5.83%.

Synthesis of (*Z*)-4-fluorotetradeca-1,3-diene (8a) from 4a

To a DMF solution (2 mL) of $\text{Pd}(\text{PPh}_3)_4$ (28.9 mg, 0.025 mmol) were added a DMF solution (1 mL) of **4a** (238 mg, 0.5 mmol) and tributylvinylstannane (174 mg, 0.55 mmol) at room temperature. After stirring at room temperature for 96 h, the reaction mixture was poured into 3 M aq. NH_4Cl (15 mL) and extracted with ether (10 mL) three times. The combined organic phase was dried over MgSO_4 and concentrated under reduced pressure. The product **8a** was isolated by column chromatography (silica gel; hexane) in 69% yield (73 mg, $Z/E = 99/1$).

Synthesis of 8 from 6

Typical Procedure: To a DMF solution (3 mL) of $\text{PdCl}_2(\text{PPh}_3)_2$ (25 mg, 0.035 mmol) were added **6a** (156 mg, 0.5 mmol) and tributylvinylstannane (270

mg, 0.85 mmol) at room temperature. The reaction mixture was stirred at 60 °C for 0.5 h, then poured into 3 M aq. NH₄Cl (15 mL) and extracted with ether (10 mL) three times. The combined organic phase was dried over MgSO₄ and concentrated under reduced pressure. The product **8a** was isolated by column chromatography (silica gel; hexane) in 86% yield (91 mg, *Z/E* ≥ 99 / 1).

(*Z*)-4-Fluorotetradeca-1,3-diene (8a).

Oil, $\delta_{\text{H}}(\text{CDCl}_3)$ 0.88 (3H, t, *J* 7.1 Hz, 14-C), 1.23-1.35 (14H, m), 1.47-1.54 (2H, m, 6-H), 2.19 (2H, dt, *J* 7.6, $^3J_{\text{H-F}}$ 17.5 Hz, 5-H), 4.95 (1H, d, *J* 10.5 Hz, 1-H), 5.10 (1H, dd, *J* 1.7, 17.1 Hz, 1-H), 5.25 [1H, dd, *J* 10.5, $^3J_{\text{H-F(olefin)}}$ 35.6 Hz, 3-H], 6.59 (1H, dt, *J* 10.5, 17.1 Hz, 2-H); $\delta_{\text{F}}(\text{CDCl}_3)$ -103.74 [1F, dt, $^3J_{\text{H-F}}$ 17.5, $^3J_{\text{H-F(olefin)}}$ 35.6 Hz]; $\delta_{\text{C}}(\text{CDCl}_3)$ 14.10, 22.69, 26.07, 28.95, 29.32 (2C), 29.51, 29.58, 31.90, 32.00 (d, $^2J_{\text{C-F}}$ 25.6 Hz, 5-C), 106.91 (d, $^2J_{\text{C-F}}$ 11.5 Hz, 3-C), 114.62 (d, $^4J_{\text{C-F}}$ 3.3 Hz, 1-C), 128.70 (d, $^3J_{\text{C-F}}$ 6.6 Hz, 2-C), 161.13 (d, $^1J_{\text{C-F}}$ 266.6 Hz, 4-C); $\nu(\text{neat})/\text{cm}^{-1}$ 3088, 2955, 2926, 2855, 1684, 1467, 1418, 1133, 994, 899, 861; [HR EI-MS: Calc. for C₁₄H₂₅F (*M*): 212.1940. Found: M⁺, 212.1933].

(1*Z*,3*E*)-1-Fluoro-1,4-diphenylbuta-1,3-diene (8b).

M.p. 132.5-133.0 °C, $\delta_{\text{H}}(\text{CDCl}_3)$ 6.29 [1H, dd, *J* 11.0, $^3J_{\text{H-F(olefin)}}$ 34.8 Hz, 2-H], 6.66 (1H, d, *J* 15.8 Hz, 4-H), 7.21-7.60 (11H, m); $\delta_{\text{F}}(\text{CDCl}_3)$ -118.26 [1F, d, $^3J_{\text{H-F(olefin)}}$ 34.8 Hz]; $\delta_{\text{C}}(\text{CDCl}_3)$ 106.91 (d, $^2J_{\text{C-F}}$ 13.3 Hz, 2-C), 120.93 (d, $^3J_{\text{C-F}}$ 5.0 Hz, 3-C), 123.94 (2C, d, $^3J_{\text{C-F}}$ 7.4 Hz, ortho), 126.48 (2C), 127.70, 128.59 (2C), 128.66 (2C), 128.90, 132.01 (d, $^3J_{\text{C-F}}$ 26.4 Hz, ipso), 132.26 (d, $^4J_{\text{C-F}}$ 3.3 Hz, 4-C), 137.29, 157.04 (d, $^1J_{\text{C-F}}$ 255.3 Hz, 1-C); $\nu(\text{KBr})/\text{cm}^{-1}$ 3060, 3033, 3020, 2997, 1634, 1488, 1444, 1320, 1280, 994, 965, 863, 748, 687, 653, 617; [HR EI-MS: Calc. for C₁₆H₁₃F (*M*): 224.1001. Found: M⁺, 224.1005].

Synthesis of (*Z*)-2-fluoro-1-phenyldodec-1-ene (9a) from 4a

To a mixture of Pd(OAc)₂ (5.6 mg, 0.025 mmol), KI (4.2 mg, 0.025

mmol) and phenylboronic acid (67 mg, 0.55 mmol) in benzene (5 mL) were added 2 M aq. K_2CO_3 (0.3 mL, 0.6 mmol) and a benzene solution (2 mL) of **4a** (238 mg, 0.5 mmol) at room temperature. After stirring at room temperature for 2 h, the reaction mixture was poured into 3 M aq. NH_4Cl (15 mL) and extracted with ether (10 mL) three times. The combined organic phase was dried over MgSO_4 and concentrated under reduced pressure. The product **9a** was isolated by column chromatography (silica gel; hexane) in 36% yield (47 mg, *Z*/*E* = 76 / 24).

Synthesis of **9** from **6**

Typical Procedure: To a mixture of $\text{PdCl}_2(\text{PPh}_3)_2$ (18 mg, 0.025 mmol) and phenylboronic acid (73 mg, 0.6 mmol) in benzene (5 mL) were added 2 M aq. K_2CO_3 (0.3 mL, 0.6 mmol) and **6a** (156 mg, 0.5 mmol) at room temperature. After stirring at 80 °C for 1.5 h, the reaction mixture was poured into 3 M aq. NH_4Cl (15 mL) and extracted with diethyl ether (10 mL) three times. The combined organic phase was dried over MgSO_4 and concentrated under reduced pressure. The product **9a** was isolated by column chromatography (silica gel; hexane) in 88% yield (112 mg, *Z* isomer only).

(*Z*)-2-Fluoro-1-phenyldodec-1-ene (**9a**).

Oil, $\delta_{\text{H}}(\text{CDCl}_3)$ 0.88 (3H, t, J 6.7 Hz, 12-H), 1.21-1.63 (16H, m), 2.31 (2H, dt, J 7.6, $^3J_{\text{H-F}}$ 18.3 Hz, 3-H), 5.45 [1H, d, $^3J_{\text{H-F(olefin)}}$ 39.5 Hz], 7.17-7.47 (5H, m, Ph); $\delta_{\text{F}}(\text{CDCl}_3)$ -101.25 [1F, dt, $^3J_{\text{H-F}}$ 18.3, $^3J_{\text{H-F(olefin)}}$ 39.5 Hz]; $\delta_{\text{C}}(\text{CDCl}_3)$ 14.13, 22.69, 26.39, 28.84, 29.12, 29.17, 29.33, 29.52, 29.59, 31.91, 108.04 (d, $^2J_{\text{C-F}}$ 28.9 Hz, 1-C), 126.55 (2C), 128.42 (3C), 134.43 (d, $^3J_{\text{C-F}}$ 14.1 Hz, ipso), 162.78 (d, $^1J_{\text{C-F}}$ 253.1 Hz, 2-C); $\nu(\text{neat})/\text{cm}^{-1}$ 3059, 3026, 2926, 2854, 1691, 1496, 1466, 1346, 1149, 912, 882, 831, 751, 693; [HR EI-MS: Calc. for $\text{C}_{18}\text{H}_{27}\text{F}$ (*M*): 262.2097. Found: M^+ , 262.2094].

(*Z*)-2-Fluoro-1,2-diphenylethene (**9b**).

M.p. 92.5-93.2 °C, $\delta_{\text{H}}(\text{CDCl}_3)$ 6.31 [1H, d, $^3J_{\text{H-F(olefin)}}$ 39.5 Hz, 2-H], 7.23-7.65

(10H, m); $\delta_{\text{F}}(\text{CDCl}_3)$ -114.78 [1F, d, $^3J_{\text{H-F(olefin)}}$ 39.5 Hz]; $\delta_{\text{C}}(\text{CDCl}_3)$ 105.83 (d, $^2J_{\text{C-F}}$ 9.9 Hz, 2-C), 124.27 (2C, d, $^3J_{\text{C-F}}$ 7.4 Hz, ortho), 127.30 (2C, d, $^4J_{\text{C-F}}$ 2.5 Hz, meta), 128.57 (3C), 128.89, 128.98 (2C), 132.85 (d, $^2J_{\text{C-F}}$ 28.1 Hz, ipso), 133.65 (d, $^3J_{\text{C-F}}$ 3.3 Hz, ipso), 157.18 (d, $^1J_{\text{C-F}}$ 258.5 Hz, 1-C); $\nu(\text{KBr})/\text{cm}^{-1}$ 3089, 3054, 3020, 1653, 1494, 1449, 1333, 1282, 1199, 1077, 1033, 1011, 913, 830, 762, 687, 626; [HR EI-MS: Calc. for $\text{C}_{14}\text{H}_{11}\text{F}$ (M): 198.0845. Found: M^+ , 198.0845].

Synthesis of (*Z*)-8-fluorooctadec-7-en-5-yne (**10a**) from **4a**

A DMF solution (5 mL) of $\text{Pd}(\text{OAc})_2$ (5.6 mg, 0.025 mmol) and PPh_3 (13.1 mg, 0.05 mmol) was stirred at room temperature for 10 min and then CuI (15.2 mg, 0.08 mmol), hex-1-yne (49 mg, 0.6 mmol), Et_3N (76 mg, 0.75 mmol) and a DMF solution (1 mL) of **4a** (238 mg, 0.5 mmol) were added. After stirring for 15 min at room temperature, the reaction mixture was poured into 3 M aq. NH_4Cl (15 mL), and extracted with ether (10 mL) three times. The combined organic phase was dried over MgSO_4 and concentrated under reduced pressure. The product **10a** was isolated by column chromatography (silica gel; hexane) in 65% yield (86 mg, *Z* isomer only).

Synthesis of **10** from **6**

Typical Procedure: A mixture of $\text{Pd}(\text{OAc})_2$ (5.6 mg, 0.025 mmol) and PPh_3 (13 mg, 0.05 mmol) in DMF (5 mL) was stirred at room temperature for 10 min and then CuI (15 mg, 0.08 mmol), hex-1-yne (62 mg, 0.75 mmol), Et_3N (150 mg, 1.5 mmol) and **6a** (156 mg, 0.5 mmol) were added. After stirring at 30 °C for 2 h, the reaction mixture was poured into 3 M aq. NH_4Cl (15 mL) and extracted with ether (10 mL) three times. The combined organic phase was dried over MgSO_4 and concentrated under reduced pressure. The product **10a** was isolated by column chromatography (silica gel; hexane) in 88% yield (117 mg, *Z* isomer only).

(*Z*)-8-Fluorooctadec-7-en-5-yne (10a).

Oil, $\delta_{\text{H}}(\text{CDCl}_3)$ 0.86-0.93 (6H, m), 1.22-1.55 (20H, m), 2.20 (2H, dt, $^3J_{\text{H-F}}$ 17.1, J 7.6 Hz, 9-H), 2.33 (2H, t, J 7.1 Hz, 4-H), 4.75 [1H, d, $^3J_{\text{H-F(olefin)}}$ 34.1 Hz, 7-H]; $\delta_{\text{F}}(\text{CDCl}_3)$ -92.08 [1F, dt, $^3J_{\text{H-F}}$ 17.1, $^3J_{\text{H-F(olefin)}}$ 34.1 Hz]; $\delta_{\text{C}}(\text{CDCl}_3)$ 13.59, 14.10, 19.23, 21.94, 22.66, 25.91, 28.84, 29.25, 29.28, 29.46, 29.55, 30.81, 31.87, 31.93 (d, $^2J_{\text{C-F}}$ 24.8 Hz, 9-C), 72.40 (d, $^4J_{\text{C-F}}$ 3.2 Hz, 5-C), 87.51 (d, $^2J_{\text{C-F}}$ 14.9 Hz, 7-C), 94.00 (d, $^3J_{\text{C-F}}$ 5.7 Hz, 6-C), 168.75 (d, $^1J_{\text{C-F}}$ 268.5 Hz, 8-C); $\nu(\text{neat})/\text{cm}^{-1}$ 2957, 2927, 2856, 2221, 1674, 1466, 1332, 1261, 1165, 1103, 873, 801; [HR EI-MS: Calc. for $\text{C}_{18}\text{H}_{31}\text{F}$ (M): 266.2410. Found: M^+ , 266.2406]. Found: C, 80.99; H, 11.45%. Calcd for $\text{C}_{18}\text{H}_{31}\text{F}$: C, 81.14; H, 11.73%.

(*Z*)-1-Fluoro-1-phenylocta-1-en-3-yne (10b).

Oil, $\delta_{\text{H}}(\text{CDCl}_3)$ 0.94 (3H, t, J 7.3 Hz, 8-H), 1.44-1.61 (4H, m), 2.40-2.44 (2H, m, 5-H), 5.57 [1H, dt, $^5J_{\text{H-H}}$ 2.4, $^3J_{\text{H-F(olefin)}}$ 33.4 Hz, 2-H], 7.34-7.54 (5H, m, Ph); $\delta_{\text{F}}(\text{CDCl}_3)$ -106.77 [1F, d, $^3J_{\text{H-F(olefin)}}$ 33.4 Hz]; $\delta_{\text{C}}(\text{CDCl}_3)$ 13.60, 19.53, 21.96, 30.76, 73.11 (d, $^4J_{\text{C-F}}$ 3.3 Hz, 4-C), 87.60 (d, $^2J_{\text{C-F}}$ 16.6 Hz, 2-C), 97.84 (d, $^3J_{\text{C-F}}$ 5.8 Hz, 3-C), 123.91 (2C, d, $^3J_{\text{C-F}}$ 7.4 Hz, ortho), 128.58 (2C, d, $^4J_{\text{C-F}}$ 1.6 Hz, meta), 129.63, 131.29 (d, $^2J_{\text{C-F}}$ 26.4 Hz, ipso), 164.15 (d, $^1J_{\text{C-F}}$ 258.6 Hz, 1-C); $\nu(\text{neat})/\text{cm}^{-1}$ 3058, 2958, 2932, 2872, 2221, 1643, 1496, 1448, 1326, 1286, 1038, 1018, 830, 760, 688; [HR EI-MS: Calc. for $\text{C}_{14}\text{H}_{15}\text{F}$ (M): 202.1158. Found: M^+ , 202.1148]. Found: C, 82.85; H, 7.61%. Calcd for $\text{C}_{14}\text{H}_{15}\text{F}$: C, 83.13; H, 7.47%.

Synthesis of methyl (*Z*)-3-fluorotridec-2-enoate (11a) from 4a

In a glass round-bottom flask fitted with a balloon (3 L) were placed PdCl_2 (1.8 mg, 0.01 mmol), NaHCO_3 (42 mg, 0.5 mmol) and MeOH (4 mL). After the complete replacement of the atmosphere in the flask with CO, the balloon was filled with CO. Then a MeOH solution (1 mL) of **4a** (238 mg, 0.5 mmol) was added and the mixture was stirred at room temperature for 2 h. The reaction mixture was poured into 3 M aq. NH_4Cl (15 mL) and

extracted with ether (10 mL) three times. The combined organic phase was dried over MgSO_4 and concentrated under reduced pressure. The product **11a** was isolated by column chromatography (silica gel; hexane-diethyl ether) in 73% yield (89 mg, $Z/E \geq 99/1$).

Under the same reaction conditions, methyl (*E*)-tridec-2-enoate ($E/Z \geq 99/1$) and methyl (*E*)-3-fluorotridec-2-enoate ($E/Z = 98/2$) were prepared from (*E*)-dodec-1-enyl(phenyl)iodonium tetrafluoroborate (**15**) (90%) and (*E*)-2-fluorododec-1-enyl(phenyl)iodonium tetrafluoroborate (**14**) (91%), respectively.

Synthesis of **11** from **6**

Typical Procedure: In a round-glass flask fitted with a balloon (3 L) were placed $\text{PdCl}_2(\text{PPh}_3)_2$ (7.0 mg, 0.01 mmol), Et_3N (50 mg, 0.5 mmol) and MeOH (5 mL). After the complete replacement of the atmosphere in the flask with CO, the balloon was filled with CO, and **6a** (156 mg, 0.5 mmol) was added into the flask. After stirring at 60 °C for 48 h, the reaction mixture was poured into 3 M aq. NH_4Cl (15 mL) and extracted with ether (10 mL) three times. The combined organic phase was dried over MgSO_4 and concentrated under reduced pressure. The product **11a** was isolated by column chromatography (silica gel; hexane-ether) in 88% yield (107 mg, $Z/E \geq 99/1$).

Methyl (*Z*)-3-fluorotridec-2-enoate (**11a**).

Oil, $\delta_{\text{H}}(\text{CDCl}_3)$ 0.88 (3H, t, J 7.1 Hz, 13-H), 1.21-1.37 (14H, m) 1.52-1.59 (2H, m, 5-H), 2.26 (2H, dt, $^3J_{\text{H-F}}$ 17.3, J 7.6 Hz, 4-H), 3.72 (3H, s, OMe), 5.18 [1H, d, $^3J_{\text{H-F(olefin)}}$ 33.1 Hz, 2-H]; $\delta_{\text{F}}(\text{CDCl}_3)$ -79.53 [1F, dt, $^3J_{\text{H-F}}$ 17.3, $^3J_{\text{H-F(olefin)}}$ 33.1 Hz]; $\delta_{\text{C}}(\text{CDCl}_3)$ 14.11, 22.68, 25.54, 28.80, 29.21, 29.29, 29.42, 29.53, 31.88, 32.98 (d, $^2J_{\text{C-F}}$ 24.1 Hz, 4-C), 51.33, 98.38 (d, $^2J_{\text{C-F}}$ 6.0 Hz, 2-C), 164.30, 172.40 (d, $^1J_{\text{C-F}}$ 281.1 Hz, 3-C); $\nu(\text{neat})/\text{cm}^{-1}$ 2951, 2926, 2855, 1736, 1685, 1466, 1436, 1349, 1278, 1217, 1137, 1033, 889, 833, 722; [HR EI-MS: Calc. for $\text{C}_{13}\text{H}_{22}\text{FO}$ (M - OMe): 213.1655. Found: M^+ - OMe, 213.1648].

Found: C, 68.78; H, 10.42%. Calcd for C₁₄H₂₅FO₂: C, 68.82; H, 10.31%.

Methyl (*Z*)-3-fluoro-3-phenylprop-2-enoate (11b).

Oil, $\delta_{\text{H}}(\text{CDCl}_3)$ 3.80 (3H, s, COOMe), 5.92 [1H, d, $^3J_{\text{H-F(olefin)}}$ 33.4 Hz, 2-H], 7.42-7.68 (5H, m, Ph); $\delta_{\text{F}}(\text{CDCl}_3)$ -96.25 [1F, d, $^3J_{\text{H-F(olefin)}}$ 33.4 Hz]; $\delta_{\text{C}}(\text{CDCl}_3)$ 51.59, 96.75 (d, $^2J_{\text{C-F}}$ 7.4 Hz, 2-C), 125.61 (2C, $^3J_{\text{C-F}}$ 8.2 Hz, ortho), 128.86 (2C), 130.51 (d, $^2J_{\text{C-F}}$ 25.60 Hz, ipso), 131.55, 164.48, 166.41 (d, $^1J_{\text{C-F}}$ 277.6 Hz, 3-C); $\nu(\text{neat})/\text{cm}^{-1}$ 3090, 2997, 2952, 2844, 1727, 1662, 1496, 1450, 1435, 1339, 1285, 1192, 1167, 1057, 1004, 828, 770, 688; [HR EI-MS: Calc. for C₁₀H₉FO₂ (*M*): 180.0586. Found: M⁺, 180.0586]. Found: C, 66.51; H, 5.17%. Calcd for C₁₀H₉FO₂: C, 66.66; H, 5.03%.

1,2,2-Trifluorododecane (12).

Oil, $\delta_{\text{H}}(\text{CDCl}_3)$ 0.88 (3H, t, *J* 6.8 Hz, 12-H), 1.27-1.56 (16H, m), 1.87-2.00 (2H, m, 3-H), 4.42 (2H, dt, $^3J_{\text{H-F}}$ 11.4, $^2J_{\text{H-F}}$ 46.6 Hz, 1-H); $\delta_{\text{F}}(\text{CDCl}_3)$ -234.95 - -235.29 (1F, m), -109.44 - -109.64 (2F, m); $\delta_{\text{C}}(\text{CDCl}_3)$; 14.10, 21.54 (t, $^3J_{\text{C-F}}$ 4.1 Hz, 4-C), 22.68, 29.30 (3C), 29.43, 29.55, 31.89, 33.03 (t, $^2J_{\text{C-F}}$ 23.9 Hz, 3-C), 81.49 (dt, $^2J_{\text{C-F}}$ 37.1, $^1J_{\text{C-F}}$ 177.6 Hz, 1-C), 121.09 (dt, $^2J_{\text{C-F}}$ 22.3, $^1J_{\text{C-F}}$ 241.2 Hz, 2-C); $\nu(\text{neat})/\text{cm}^{-1}$ 2960, 2926, 2856, 1466, 1381, 1280, 1196, 1137, 1060, 928; [HR EI-MS: Calc. for C₁₂H₂₃F₃ (*M*): 224.1752. Found: M⁺, 224.1768].

Preparation of (*E*)-2-fluorododec-1-enyl(phenyl)iodonium tetrafluoroborate (14)

To a CH₂Cl₂ solution (6 mL) of dodec-1-yne (332 mg, 2 mmol) was added an Et₃N·5HF solution (22 mL) of *p*-iodotoluene difluoride (768 mg, 3 mmol) at 0 °C and the mixture was stirred at 0 °C for 2 h. The reaction mixture was poured into water (30 mL) and extracted with CH₂Cl₂ (20 mL) three times. The combined organic phase was dried over MgSO₄ and concentrated under reduced pressure. The resulting crude (*E*)-2-fluorododec-1-enyl(phenyl)iodonium fluoride^{5a,c} was dissolved in

acetonitrile (10 mL) with AgBF₄ (779 mg, 4 mmol) and the mixture was stirred at room temperature for 1 h. The reaction mixture was poured into water (30 mL) and extracted with CH₂Cl₂ (20 mL) three times. The combined organic phase was dried over MgSO₄ and concentrated under reduced pressure. The resulting viscous oil was dissolved in CH₂Cl₂ (1 mL) and a white suspension was formed by the addition of hexane (40 mL). The white suspension was left in a refrigerator for 2 h and clear upper liquid was removed by decantation. The remained white solid was washed with hexane (5 mL) again, separated by decantation, and dried in vacuo to give pure (*E*)-2-fluorododec-1-enyl(phenyl)iodonium tetrafluoroborate (**14**) (43%, 400 mg, 0.84 mmol).

M.p. 71.8-72.4 °C, δ_{H} (CDCl₃); 0.88 (3H, t, J 6.8 Hz, 12-H), 1.17-1.30 (14H, m), 1.47-1.54 (2H, m, 4-H), 2.79 (2H, dt, J 7.6, $^3J_{\text{H-F}}$ 22.2 Hz, 3-H), 6.72 [1H, d, $^3J_{\text{H-F(olefin)}}$ 14.4 Hz, 1-H], 7.46-7.98 (5H, m, Ph); δ_{F} (CDCl₃) -65.89 [1F, dt, $^3J_{\text{H-F(olefin)}}$ 14.4, $^3J_{\text{H-F}}$ 22.2 Hz]; δ_{C} (CDCl₃) 14.09, 22.64, 25.77, 28.89, 29.18, 29.26, 29.32, 29.46, 31.83, 32.16 (d, $^2J_{\text{C-F}}$ 23.9 Hz, 3-C), 78.25 (d, $^2J_{\text{C-F}}$ 47.9 Hz, 1-C), 112.10, 132.28 (2C), 132.53, 134.52 (2C), 176.22 (d, $^1J_{\text{C-F}}$ 286.5 Hz, 2-C); ν (KBr)/cm⁻¹ 3045, 2925, 2854, 1638, 1467, 1440, 1303, 1071, 993, 877, 797, 736, 684; [HR FAB-MS: Calc. for C₁₈H₂₇FI (*M* - BF₄): 389.1142. Found: M⁺ - BF₄, 389.1154]. Found: C, 45.47; H, 5.57%. Calcd for C₁₈H₂₇BF₅I: C, 45.41; H, 5.72%.

(*E*)-Dodec-1-enyl(phenyl)iodonium tetrafluoroborate (15).

M.p. 36.0-36.5 °C, δ_{H} (CDCl₃) 0.88 (3H, t, J 7.1 Hz, 12-H), 1.19-1.32 (14H, m), 1.41-1.48 (2H, m, 4-H), 2.31-2.36 (2H, m, 3-H), 6.79 (1H, d, J 13.7 Hz, 1-H), 6.99 (1H, dt, J 7.3, 13.7 Hz, 2-H), 7.48-8.02 (5H, m, Ph); δ_{C} (CDCl₃) 14.09, 22.64, 27.64, 28.91, 29.15, 29.26, 29.43, 29.50, 31.84, 35.32, 96.45, 109.58, 132.36 (2C), 132.68, 135.59 (2C), 155.40; ν (KBr)/cm⁻¹ 3052, 3002, 2918, 2850, 1469, 1444, 1067, 988, 739; [HR FAB-MS: Calc. for C₁₈H₂₈I (*M* - BF₄): 371.1236. Found: M⁺ - BF₄, 371.1220].

Synthesis of (5*E*,7*Z*)-8-fluorooctadeca-5,7-diene (16a) and (1*Z*,3*E*)-1-fluoro-1-phenylocta-1,3-diene (16b) from 6

Typical Procedure: To a mixture of Pd(PPh₃)₄ (29 mg, 0.025 mmol) and (*E*)-hex-1-enylboronic acid (77 mg, 0.6 mmol) in benzene (5 mL) were added a EtOH solution (0.5 mL) of KOH (56 mg, 1 mmol) and **6a** (156 mg, 0.5 mmol) at room temperature. After stirring for 1 h at 80 °C, the reaction mixture was poured into 3 M aq. NH₄Cl (15 mL), and extracted with diethyl ether (10 mL) three times. The combined organic phase was dried over MgSO₄ and concentrated under reduced pressure. (5*E*,7*Z*)-8-Fluorooctadeca-1,3-diene (**16a**) was isolated by column chromatography (silica gel; hexane) in 83% yield (111 mg, *Z* isomer only).

(5*E*,7*Z*)-8-Fluorooctadeca-5,7-diene (16a).

Oil, $\delta_{\text{H}}(\text{CDCl}_3)$ 0.86-0.91 (6H, m), 1.21-1.51 (20H, m), 2.05-2.21 (4H, m), 5.17 [1H, dd, J 10.7, $^3J_{\text{H-F(olefin)}}$ 36.3 Hz, 7-H], 5.57 (1H, dt, J 6.8, 15.6 Hz, 5-H), 6.22-6.29 (1H, m, 6-H); $\delta_{\text{F}}(\text{CDCl}_3)$ -106.88 [1F, dt, $^3J_{\text{H-F}}$ 17.7, $^3J_{\text{H-F(olefin)}}$ 36.3 Hz]; $\delta_{\text{C}}(\text{CDCl}_3)$ 13.93, 14.11, 22.24, 22.69, 26.23, 28.99, 29.33, 29.36, 29.53, 29.60, 31.89, 32.02 (d, $^2J_{\text{C-F}}$ 26.4 Hz, 9-C), 32.15, 32.50, 106.28 (d, $^2J_{\text{C-F}}$ 12.3 Hz, 7-C), 121.66 (d, $^3J_{\text{C-F}}$ 5.8 Hz, 6-C), 132.34, 159.23 (d, $^1J_{\text{C-F}}$ 260.2 Hz, 8-C); $\nu(\text{neat})/\text{cm}^{-1}$ 3039, 2956, 2925, 2855, 1685, 1635, 1466, 1137, 969, 850, 722; [HR EI-MS: Calc. for C₁₈H₃₃F (M): 268.2566. Found: M⁺, 268.2561].

(1*Z*,3*E*)-1-Fluoro-1-phenylocta-1,3-diene (16b).

Oil, $\delta_{\text{H}}(\text{CDCl}_3)$ 0.92 (3H, t, J 7.1 Hz, 8-H), 1.30-1.46 (4H, m), 2.17 (2H, dt, J 7.1, 7.1 Hz, 5-H), 5.83 (1H, dt, J 7.1, 15.3 Hz, 4-H), 6.05 [1H, dd, J 10.7, $^3J_{\text{H-F(olefin)}}$ 35.6 Hz, 2-H], 6.48 (1H, dd, J 10.7, J 15.3 Hz, 3-H), 7.27-7.55 (5H, m, Ph); $\delta_{\text{F}}(\text{CDCl}_3)$ -121.19 [1F, d, $^3J_{\text{H-F(olefin)}}$ 35.6 Hz]; $\delta_{\text{C}}(\text{CDCl}_3)$ 13.93, 22.26, 31.42, 32.78, 106.66 (d, $^2J_{\text{C-F}}$ 14.1 Hz, 2-C), 122.06 (d, $^3J_{\text{C-F}}$ 5.8 Hz, 3-C), 123.73 (2C, d, $^3J_{\text{C-F}}$ 7.4 Hz, ortho), 128.44 (2C), 128.46, 132.41 (d, $^2J_{\text{C-F}}$ 27.2 Hz, ipso), 135.69 (d, $^4J_{\text{C-F}}$ 3.3 Hz, 4-C), 155.05 (d, $^1J_{\text{C-F}}$ 251.9 Hz, 1-C);

$\nu(\text{neat})/\text{cm}^{-1}$ 3036, 2957, 2927, 2858, 1653, 1627, 1599, 1495, 1448, 1322,
1281, 994, 969, 761, 688; [HR EI-MS: Calc. for $\text{C}_{14}\text{H}_{17}\text{F}$ (M): 204.1314.
Found: M^+ 204.1313].

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List of Publications

1. Hara, S.; Yoshida, M.; Fukuhara, T.; Yoneda, N.
“Stereo- and regio-selective addition of iodotoluene difluoride to alk-1-yne. Selective synthesis of 2-fluoro-1-iodoalk-1-enes”,
Chem. Commun., 965, 1998.
2. Hara, S.; Yamamoto, K.; Yoshida, M.; Fukuhara, T.; Yoneda, N.
“Stereoselective synthesis of (*E*)- β -fluoro- α,β -unsaturated esters by carbonylation of (*E*)-2-fluoro-1-iodo-1-alkenyliodonium salts”,
Tetrahedron Lett., 40, 7815-7818, 1999.
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6. Yoshida, M.; Ota, D.; Fukuhara, T.; Yoneda, N.; Hara, S.
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J. Chem. Soc., Perkin Trans. 1, 384-389, 2002.

7. Yoshida, M.; Nishimura, N.; Hara, S.
“Direct synthesis of alkynyl(phenyl)iodonium salts from alk-1-yne”,
Chem. Commun. 1014, 2002.

8. Yoshida, M.; Hara, S.
“Stereoselective synthesis of (*Z*)-2-fluoro-1-alkenyl(phenyl)iodonium tetrafluoroborates”,
Org. Lett. 573, 5, 2003.

9. Yoshida, M.; Komata, A; Hara, S.
“Stereoselective synthesis of (*Z*)- β -fluoro- α,β -unsaturated esters from (*Z*)-2-fluoro-1-alkenyl(phenyl)iodonium salts”,
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