THE STEREOSELECTIVE PREPARATION OF FLUORINATED DIENES *via* STILLE–LIEBESKIND CROSS-COUPLING REACTIONS

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Dedicated to the memory of Professor Miloš Hudlický.

Readily prepared fluorinated vinylstannane reagents stereoselectively undergo Stille–Liebeskind cross-coupling reactions with vinyl halides (including fluorine-containing vinyl halides) with $Pd(PPh_3)_4$/CuI catalysis.

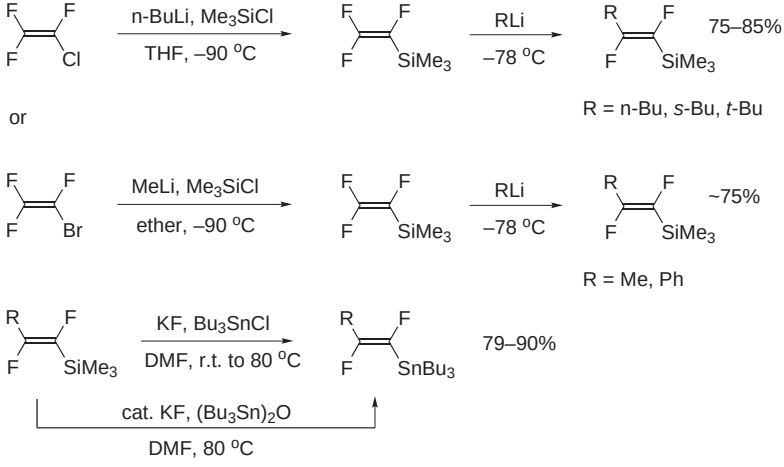
Keywords: Cross-coupling reactions; Fluorinated dienes; Stille–Liebeskind; Fluorinated vinylstannanes; Pd(0) catalysis; Alkenes; Stannanes.

Fluorine-containing compounds are of current interest in research areas such as polymer chemistry, pharmaceutical chemistry and agricultural chemistry due to the unique properties of fluorine. Replacement of a hydrogen atom by a fluorine atom is a well-established concept, largely due to the minimal structural changes brought about by such substitution. On the other hand, the differences in electronegativity between hydrogen and fluorine can alter the physical and chemical properties of the corresponding substrates[1–6].

The preparation of fluorinated dienes remains a challenge to synthetic chemists because of the difficulty of incorporating fluorine into the correct position in the molecule with a well-defined stereochemistry. Traditional methodology for the preparation of dienes, such as the Wittig reaction with α-fluoro-α,β-unsaturated aldehydes[7], suffers from difficulty in the synthesis of the starting materials and unsatisfactory stereoselectivity. Other popular methodologies for the preparation of fluorine-containing dienes include: (i) palladium(0)/copper(I) halide catalyzed coupling reactions between (1,2-difluorovinyl)stannanes and vinyl halides[8]; (ii) the coupling reaction between a fluorine-containing vinylzinc reagent and vinyl halides[9]; the coupling reaction between a fluorine-containing vinylcopper reagent with

fluorinated vinyl halides[10]; and the copper(II) salt-mediated homo-coupling of (1,2-difluorovinyl)stannanes[11].

Recently, we reported a successful stereospecific route to both (*E*)- and (*Z*)-fluorine-containing vinylstannanes[12], as illustrated in Scheme 1. These reagents underwent a Stille type coupling reaction with aryl halides and bromoacrylates under Liebeskind type conditions (Pd(0)/CuI) to form the cross-coupled products in excellent yields (81–92%)[8]. Thus, we anticipated that coupling of these (*E*)- or (*Z*)-fluorinated vinylstannanes with vinyl halides could provide a stereoselective route to fluorine-containing dienes. However, although Pd(0) catalyzed coupling between hydrogen-containing vinylstannanes and vinyl halides has already been established by Stille[13], he had also reported that the presence of strong electron-withdrawing

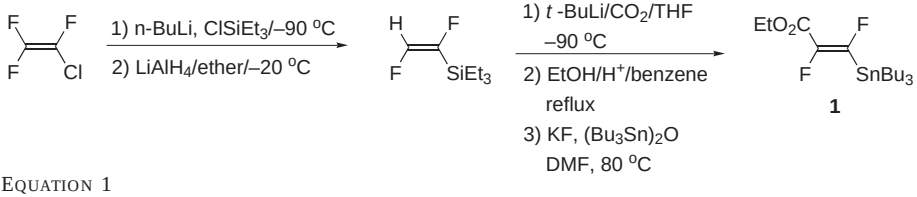


SCHEME 1

groups on the organotin reagent led to slow decomposition in coupling with aryl triflates, and no coupling was observed[14]. Thus, there was some ambiguity that the fluorine-containing vinylstannanes would function well in coupling with vinyl halides. Indeed, we have found that the fluorine-containing vinylstannanes do not readily undergo coupling with vinylic or aryl halides and Pd(0) catalysts alone. The need for Cu(I) halide as a co-catalyst (Liebeskind conditions)[15] is required for facile coupling of the fluorinated vinylstannanes[12]. Thus, our research presented herein had two major focuses: (*1*) to investigate the stereoselective preparation of fluorine-containing dienes *via* Pd(0)/CuI catalyzed coupling of fluorine-containing vinylstannanes and vinyl halides; and (*2*) to study the stability (to

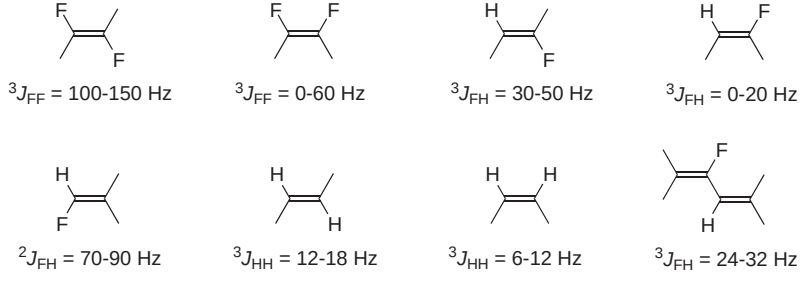
isomerization) of the resultant dienes. Previous work in our laboratory had qualitatively indicated that fluorine-containing dienes isomerize more readily than their hydrocarbon analogues.

For this particular project, we chose (*E*)-β-iodostyrene, (*Z*)-β-iodostyrene, (*Z*)-β-bromo-β-fluorostyrene, (*E*)-1-iodo-1-octene, (*Z*)-1-iodo-1-octene as model vinyl halides. We selected (*Z*)-1,2-difluoro-1-tributylstannyl-1-hexene, (*Z*)-1,2-difluoro-1-tributylstannyl-1-pentene, ethyl (*Z*)-2,3-difluoro-3-(tributylstannyl)acrylate and (*Z*)-1,2-difluoro-1-tributylstannyl-1-propene, as model fluorine-containing vinylstannanes. The ethyl (*Z*)-2,3-difluoro-3-(tributylstannyl)acrylate was prepared *via* the following route (Eq. (*1*)).



EQUATION 1

Identification of the new dienes was predominately done by detailed NMR analysis of these compounds (^{1}H, ^{19}F, ^{13}C NMR). GC-MS was also utilized to obtain information on the molecular ion. The stereochemistry of the dienes was determined by the value of the coupling constant either between two vinylic fluorines, between a vinylic hydrogen and a vinylic fluorine, or between two vinylic hydrogens[16,17]. The following *J* values (see Scheme 2) were utilized in the stereochemistry assignments.

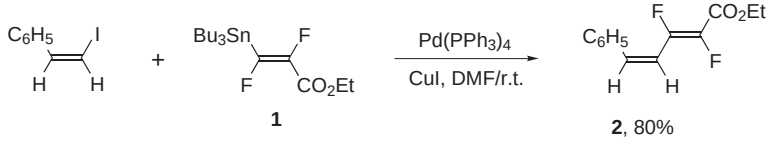


SCHEME 2

Although most of the coupling reactions proceeded readily and the diene products could be isolated in high purity by silica gel chromatography, in a few cases the isolation process was complicated by formation of small amounts of a symmetrical diene, RCF=CF–CF=CFR, formed by homo-coupling of the vinylstannanes[11]. The homo-coupled diene often could not

be readily separated from the cross-coupled dienes, thus the cross-coupled product was contaminated with small amounts of the homo-coupled diene. The ^{19}F NMR yields of the cross-coupled dienes for these less-pure dienes are presented in Table I.

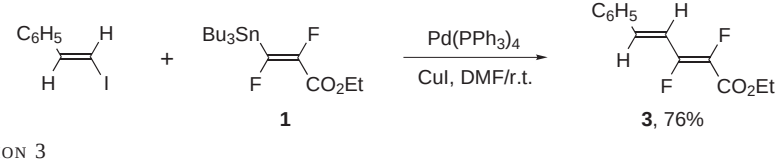
In order to assure complete consumption of the vinyl halide, a slight excess (1.2 equivalents) of the fluorinated vinylstannane was utilized in all the cross-coupling reactions. Thus, when (*Z*)-β-iodostyrene was reacted with ethyl (*Z*)-2,3-difluoro-3-(tributylstannyl)acrylate (**1**) at room temperature in DMF with CuI and $Pd(PPh_3)_4$, (Eq. (*2*)), an 80% yield of ethyl



1 **2**, 80%

EQUATION 2

(2*E*,4*Z*)-2,3-difluoro-5-phenyl-2,4-pentadienoate (**2**) was obtained. The (2*E*)-stereochemistry was readily assigned based on the $^3J_{FF}$ value of 124 Hz and the (4*Z*)-stereochemistry was readily assigned on the $^3J_{HH}$ value of 12.7 Hz. When (*E*)-β-iodostyrene was employed as the vinyl halide precursor (Eq. (*3*)), the analogous ethyl (2*E*,4*E*)-2,3-difluoro-5-phenyl-2,4-pentadienoate (**3**) was obtained in 76% isolated yield.



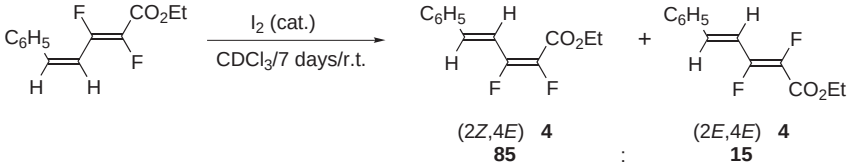
1 **3**, 76%

EQUATION 3

Again, the $^3J_{FF}$ value of 120 Hz confirmed the (4*E*)-stereochemical assignment and the $^3J_{HH}$ value of 16 Hz confirmed the (4*E*)-stereochemical assignment. Note that the $^3J_{FH}$ value of 29 and 24 Hz, respectively, permitted the assignment of the vinylic fluorine assignments and the vinylic hydrogen assignments.

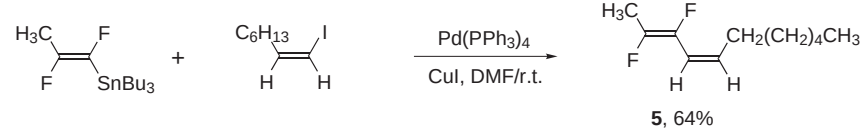
Previous work in our laboratory had indicated that a *cis*-1,2-difluoroethylenic arrangement was more stable than a *trans*-1,2-difluoroethylenic arrangement[10] and that the more stable vinylic isomer could be formed (by isomerization) from the less stable vinylic isomer either by fluoride ion catalyzed isomerization or by iodine catalyzed isomerization[18]. Consequently, when we treated ester **2** with a catalytic amount of I_2 in $CDCl_3$ (Eq. (*4*)), the isomerization of ester **2** proceeded readily (monitored by

^{19}F NMR analysis). Isolation of the resultant isomerized product yielded 74% of a mixture of the 2*Z*:4*E*/2*E*:4*E* isomers in an 85 : 15 ratio. The stereochemistry of the ethyl (2*Z*,4*E*)-2,3-difluoro-5-phenyl-2,4-pentadienoate (**4**) isomer was assigned based on the $^3J_{FF}$ value of 0 Hz (2*Z* assignment) and the $^3J_{HH}$ value of 16 Hz (4*E* assignment).



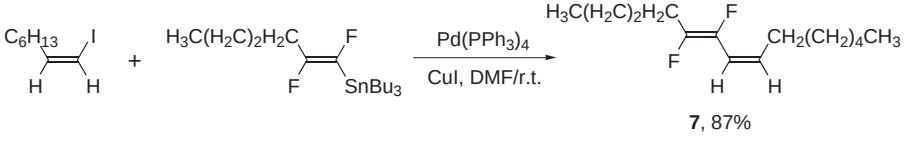
EQUATION 4

In a similar reaction, (*Z*)-1-iodo-1-octene was cross-coupled with (*Z*)-1,2-difluoro-1-tributylstannyl-1-propene to give 64% of (2*E*,4*Z*)-2,3-difluoro-2,4-undecadiene (**5**) (Eq. (*5*)). The $^3J_{FF}$ value of 121 Hz established the (2*E*)-stereochemistry, and the $^3J_{HH}$ value of 12 Hz established the (4*Z*)-stereochemistry. The $^3J_{FH}$ value of 32 Hz permitted unequivocal assignment of the vinylic fluorines and vinylic hydrogens. A similar cross-coupling reaction of (*E*)-1-iodo-1-octene with (*Z*)-1,2-difluoro-1-tributylstannyl-1-propene gave (2*E*,4*E*)-2,3-difluoro-2,4-undecadiene (**6**) in 91% yield as determined by ^{19}F NMR. However, chromatography failed to remove all the homo-coupled diene. In diene **6**, the $^3J_{FF}$ value of 117 Hz established the (2*E*)-stereochemistry and the $^3J_{HH}$ value of 16 Hz established the (4*Z*)-stereochemistry.



EQUATION 5

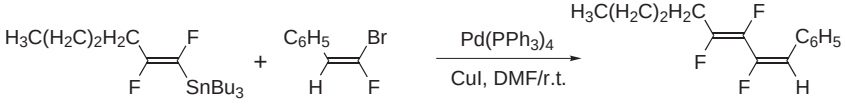
When (*Z*)-1-iodo-1-octene was cross-coupled with (*Z*)-1,2-difluoro-1-tributylstannyl-1-hexene in an analogous manner (Eq. (*6*)), an 87% yield of (5*E*,7*Z*)-5,6-difluoro-5,7-tetradecadiene (**7**) was obtained. The $^3J_{FF}$ value of



EQUATION 6

120 Hz and the $^3J_{HH}$ value of 12 Hz established the (5*E*,7*Z*)-stereochemistry. When (*E*)-1-iodo-1-octene was utilized in a similar cross-coupling with (*Z*)-1,2-difluoro-1-tributylstannyl-1-hexene, the (5*E*,7*E*)-5,6-difluoro-5,7-tetradecadiene (**8**) was obtained in 90% yield as determined by ^{19}F NMR. However, chromatography failed to separate completely the homo-coupled diene. The $^3J_{FF}$ value of 117 Hz and the $^3J_{HH}$ value of 16 Hz established the stereochemical assignments (5*E*,7*E*).

We then investigated the strategy outlined above as a potential stereospecific route to 2,3,4-trifluorodienes. Thus, when (*Z*)-β-bromo-β-fluorostyrene was reacted with (*Z*)-1,2-difluoro-1-tributylstannyl-1-propene with CuI/Pd(PPh$_3$)$_4$ catalysis, a 76% yield of (1*E*,3*E*)-2,3,4-trifluoro-1-phenyl-1,3-pentadiene (**9**) was obtained. The $^3J_{FF}$ value of 131 Hz established the (3*E*)-stereochemical assignment and the $^3J_{FH}$ value of 19 Hz established the (1*E*)-stereochemistry. The $^3J_{FH}$ value of 17 Hz and $^3J_{FF}$ value of 37 Hz established the positions of the three vinylic fluorines. The analogous (1*E*,3*E*)-2,3,4-trifluoro-1-phenyl-1,3-octadiene (**10**) was prepared from (*Z*)-β-bromo-β-fluorostyrene and (*Z*)-1,2-difluoro-1-tributylstannyl-1-hexene in 71% yield (Eq. (*7*)). As in the previous examples, $^3J_{FF}$ and $^3J_{FH}$ values were utilized to confirm the stereochemical assignments.



10, 71%

EQUATION 7

Related cross-coupling reactions, that were complicated with homo-coupling, gave compounds **11**–**14** and are summarized in Table I. Their spectroscopic data (obtained from the mixture) are summarized in the Experimental.

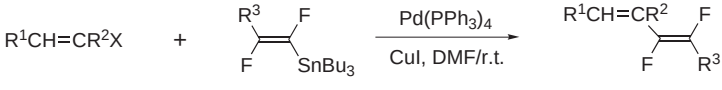
In conclusion, (1,2-difluorovinyl)stannanes readily cross-couple with vinyl iodides and bromides under Stille–Liebeskind conditions (CuI/Pd(PPh$_3$)$_4$ catalysis), and this methodology provides a useful stereoselective route to a variety of difluoro- and trifluorodienes.

EXPERIMENTAL

All reactions were monitored by ^{19}F NMR analysis of the reaction mixture either on a 90 or 300 MHz spectrometer. The ^{1}H, ^{19}F, and ^{13}C NMR spectra of final products were obtained on a 300 MHz spectrometer ($CDCl_3$, $CFCl_3$ or TMS as internal references). Chemical shifts (δ) are given in ppm, coupling constants (*J*) in Hz. GC-MS analyses were performed at 70 eV in the electron-impact mode on a single quadrupole instrument interfaced to a gas

chromatograph fitted with an OV-101 column. HRMS were obtained on a VG Analytical ZAB-HF Mass Spectrometer operated at 70 eV in the electron impact mode. Analytical GLPC analyses were performed on a 5% OV-101 column. The vinylstannanes, such as (*Z*)-1,2-difluoro-1-tributylstannyl-1-propene, (*Z*)-1,2-difluoro-1-tributylstannyl-1-pentene and (*Z*)-1,2-difluoro-1-tributylstannyl-1-hexene, were prepared by the literature procedure[12]. Vinyl halides, such as (*E*)- and (*Z*)-β-iodostyrene, and (*E*)- and (*Z*)-1-iodo-1-octene, were prepared by literature procedures[19–21]. DMF was dried by distillation over CaH_2. All organic solvents for column chromatography were purchased from Aldrich Chemicals and Fisher Scientific and used without further purification. CuI was purified by the literature procedure[22], and $Pd(PPh_3)_4$ was prepared by the literature procedure[23]. (*Z*)-1,2-Difluoro-1-(triethylsilyl)ethylene was prepared by the literature procedure[24]. All other chemicals were obtained from commercial vendors and used directly. In addition to the cross-coupled product (dienes) generally the homo-coupled product from the vinylstannane was formed in small amounts (5–10%). In most cases the homo-coupled diene could be separated from the cross-coupled product by silica gel chromatography. In the cases where the homo-coupled product could not be separated or decreased to less than 3%, the ^{19}F NMR yield is reported (using $C_6H_5CF_3$ as an internal standard). Although the homo-coupled product could not be completely separated, in most cases spectroscopic data of the cross-coupled diene could be determined unequivocally, and is reported in the experimental section. We did not see any

TABLE I
Stille–Liebeskind coupling of fluorinated vinylstannanes

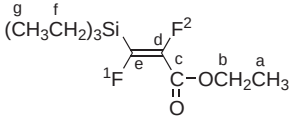


R^1	R^2	X	*E/Z*	R^3	*E/Z*	Diene	Yield, %	Diene strereochemistry
C_6H_5	H	I	*Z*	CO_2Et	*Z*	**2**	80[a]	2*E*,4*Z*
C_6H_5	H	I	*E*	CO_2Et	*Z*	**3**	76[a]	2*E*,4*E*
C_6H_{13}	H	I	*Z*	CH_3	*Z*	**5**	64[a]	2*E*,4*Z*
C_6H_{13}	H	I	*Z*	C_4H_9	*Z*	**7**	87[a]	5*E*,7*Z*
C_6H_5	F	Br	*Z*	CH_3	*Z*	**9**	76[a]	1*E*,3*E*
C_6H_5	F	Br	*Z*	C_4H_9	*Z*	**10**	71[a]	1*E*,3*E*
C_6H_5	H	I	*E*	C_4H_9	*Z*	**14**	91[b]	1*E*,3*E*
C_6H_5	H	I	*Z*	C_4H_9	*Z*	**13**	93[b]	1*Z*,3*E*
C_6H_{13}	H	I	*E*	CH_3	*Z*	**6**	80[b]	2*E*,4*E*
C_6H_{13}	H	I	*E*	CO_2Et	*Z*	**12**	90[b]	2*E*,4*E*
C_6H_{13}	H	I	*Z*	CO_2Et	*Z*	**11**	91[b]	2*E*,4*Z*
C_6H_{13}	H	I	*E*	C_4H_9	*Z*	**8**	90[b]	5*E*,7*E*

[a] Isolated yield; [b] ^{19}F NMR yield.

evidence for isomerization in any of these coupling reactions. The source of the homo-coupled product is probably from homo-coupling of the vinyl stannane by the CuI co-catalyst. Piers has reported similar homo-coupling of alkenylstannanes with CuCl [25].

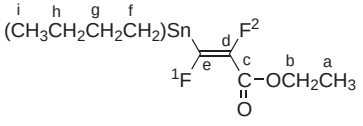
Preparation of Ethyl (*Z*)-2,3-Difluoro-3-(triethylsilyl)acrylate



A 500 ml three-necked flask equipped with a low temperature thermometer, a magnetic stir bar, a N_2 tee, and a dry-ice/acetone condenser, was charged with THF (150 ml) and ether (150 ml), 26.7 g (0.15 mol) HCF=CFSiEt$_3$ (*Z*/*E* = 95 : 5) and cooled to –95 °C with a pentane/liquid nitrogen bath. Then, *t*-BuLi (95 ml, 1.7 M in pentane, 0.16 mol) was slowly added over one hour *via* syringe. The temperature of the reaction mixture was maintained below –90 °C during the addition. After the addition was completed, the solution was stirred at –90 °C for 30 min and then carbon dioxide gas was bubbled slowly into the reaction mixture through a Pasteur pipet maintaining the internal temperature below –85 °C (*ca* 1/2 h). The reaction mixture was then warmed to room temperature (*ca* 3 h). Aqueous HCl solution (0.1 M, 100 ml) was added and the reaction mixture extracted with ether (2 × 200 ml). The combined organic layers were washed with brine and dried over $MgSO_4$. Evaporation of solvents gave crude (*Z*)-Et$_3$SiCF=CFCOOH as a yellow liquid.

The above acid was mixed with benzene (150 ml), ethanol (50 ml) and *p*-toluenesulfonic acid (1 g) and refluxed for 24 h. The resulting water was removed *via* a Dean–Stark trap. After the usual work-up, followed by purification on silica gel chromatography (ethyl acetate–hexane, 1 : 25) the titled product was obtained in 75% yield (based on (*Z*)-CHF=CFSiEt$_3$) as a colorless liquid. ^{19}F NMR ($CDCl_3$): –141.8 (d, $^3J_{FF}$ = 132.3, 1 F, F^1); –160.6 (d, $^3J_{FF}$ = 132.3, 1 F, F^2). ^{1}H NMR ($CDCl_3$): 4.34 (q, $^3J_{HH}$ = 7.2, 2 H, H^b); 1.36 (t, $^3J_{HH}$ = 7.6, 3 H, H^a); 1.01 (t, $^3J_{HH}$ = 7.6, 9 H, H^g); 0.80 (q, $^3J_{HH}$ = 7.6, 6 H, H^f). ^{13}C NMR ($CDCl_3$): 167.9 (dd, $^1J_{CF}$ = 299.1, $^2J_{CF}$ = 73.4, C^d or C^e); 159.0 (dd, $^2J_{CF}$ = 34.2, $^3J_{CF}$ = 2.5, C^c); 150.9 (dd, $^1J_{CF}$ = 233.2, $^2J_{CF}$ = 30.6, C^e or C^d); 61.5 (s, C^b); 14.0 (s, C^a); 6.9 (s, C^g); 2.0 (d, $^3J_{CF}$ = 1.9, C^f). HRMS: calculated for $C_{10}H_{17}F_2O_2Si$ (M^+ – Me): 235.0966; found: 235.0966. Calculated for $C_{10}H_{15}F_2O_2Si$ (M^+ – Et): 221.0809; found: 221.0803.

Preparation of Ethyl (*Z*)-2,3-Difluoro-3-(tributylstannyl)acrylate (**1**)



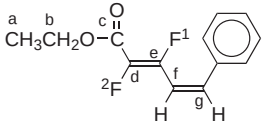
A 100 ml round bottom flask, equipped with a N_2 tee, a condenser and a magnetic stir bar, was charged with dry DMF (20 ml), freshly dried potassium fluoride (0.10 g, 1.7 mmol), tributyltin oxide (3.0 g, 5.0 mmol) and ethyl (*Z*)-2,3-difluoro-3-(triethylsilyl)acrylate (2.50 g,

10 mmol). The mixture was stirred at 80 °C for 10 h (the starting material had completely disappeared by ^{19}F NMR analysis of the reaction mixture). The reaction mixture was treated with water (50 ml) and extracted with diethyl ether (2 × 50 ml). The combined ether layers were washed with water, dried, and concentrated. The residue was purified on a silica gel column (hexane–ethyl acetate, 30 : 1) to give 3.0 g (70%) of ester **1** as a slightly yellow oil. ^{19}F NMR ($CDCl_3$): –129.2 (d, $^3J_{FF}$ = 122.1, 1 F, F^1); –162.6 (d, $^1J_{FF}$ = 122.1, 1 F, F^2). ^{13}C NMR ($CDCl_3$): 175.9 (dd, $^1J_{CF}$ = 337.5, $^2J_{CF}$ = 97.0, C^d or C^e); 158.5 (d, $^2J_{CF}$ = 56.0, C^c); 150.8 (dd, $^1J_{CF}$ = 220.3, $^2J_{CF}$ = 22.5, C^e or C^d); 61.3 (s, C^b); 28.6 (s, C^f); 27.1 (s, C^g); 14.1 (s, C^a); 13.5 (s, C^h); 10.3 (s, C^i). HRMS: calculated for $C_{13}H_{23}F_2O_2Sn$ (M^+ – Bu): 369.0688; found: 369.0658.

Representative Procedure for the Preparation of Dienes

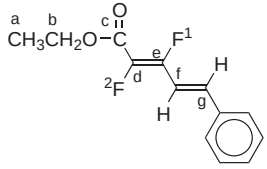
A 25 ml round bottom flask, equipped with a stir bar and a N_2 tee, was charged with $Pd(PPh_3)_4$ (0.05 g, 0.043 mmol), CuI (0.10 g, 0.50 mmol), vinyl iodide (or β-bromo-β-fluoroolefin) (1.0 mmol) and dry DMF (5 ml) and then the vinylstannane (1.2 mmol) was added at room temperature with stirring. The resulting mixture was stirred overnight at room temperature and no starting fluorinated stannane remained by ^{19}F NMR analysis of the reaction mixture. The reaction mixture was diluted with diethyl ether (100 ml) and washed with aqueous KF solution (15%, 50 ml). The organic layer was separated and dried over $MgSO_4$. The ether was removed by rotary evaporator, and the residue was purified by silica gel column chromatography (for unfunctionalized dienes, hexanes used as eluent; for functionalized dienes, hexanes–ethyl acetate, 97 : 3, used as the eluent).

Ethyl (2E,4Z)-2,3-Difluoro-5-phenyl-2,4-pentadienoate (**2**)



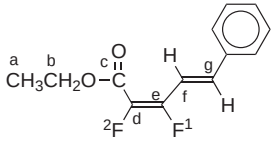
Similarly, the reaction of (*Z*)-β-iodostyrene (0.23 g, 1.0 mmol) with ethyl (*Z*)-2,3-difluoro-3-(tributylstannyl)acrylate (0.50 g, 1.2 mmol) in dry DMF (5 ml), with CuI (0.10 g, 0.5 mmol) and $Pd(PPh_3)_4$ (0.05 g, 0.043 mmol) gave 0.19 g (80%) of ester **2**, 98% purity. ^{19}F NMR ($CDCl_3$): –131.9 (dd, $^3J_{FF}$ = 124.0, $^3J_{FH}$ = 28.7, 1 F, F^1); –158.5 (dd, $^3J_{FF}$ = 124.6, $^4J_{FH}$ = 5.0, 1 F, F^2). ^1H NMR ($CDCl_3$): 7.24–7.32 (m, aromatic hydrogens, 5 H); 6.83 (dt, $^3J_{HH}$ = 12.7, $^4J_{HF}$ = 1.3, 1 H, H^g); 6.25 (ddd, $^3J_{HF}$ = 28.8, $^3J_{HH}$ = 12.7, $^4J_{HF}$ = 5.5, 1 H, H^f); 4.26 (q, $^3J_{HH}$ = 7.0, 2 H, H^b); 1.26 (t, $^3J_{HH}$ = 7.2, 3 H, H^a). ^{13}C NMR ($CDCl_3$): 159.7 (dd, $^2J_{CF}$ = 29.4, $^3J_{CF}$ = 6.0, C^c); 155.9 (dd, $^1J_{CF}$ = 261.3, $^2J_{CF}$ = 42.5, C^d or C^e); 138.1 (dd, $^1J_{CF}$ = 244.9, $^2J_{CF}$ = 39.3, C^e or C^d); 135.7 (dd, $^3J_{FF}$ = 6.2, $^4J_{CF}$ = 5.1, C^g); 134.8 (d, J_{CF} = 1.4, aromatic carbon); 129.8 (s, aromatic carbon); 128.9 (s, aromatic carbon); 127.7 (d, J_{CF} = 1.1, aromatic carbon); 113.2 (dd, $^2J_{CF}$ = 17.4, $^3J_{CF}$ = 0.7, C^f); 61.6 (s, C^b); 14.1 (s, C^a). GC-MS (EI, *m/z* (rel.%)): 238 (50) [M^+], 218 (7), 190 (23), 173 (84), 165 (100) [$M^+ - CO_2Et$], 145 (55), 133 (35), 115 (26).

Ethyl (2E,4E)-2,3-Difluoro-5-phenyl-2,4-pentadienoate (**3**)



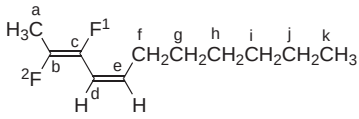
Similarly, the reaction of (*E*)-β-iodostyrene (0.23 g, 1.0 mmol) with ethyl (*Z*)-2,3-difluoro-3-(tributylstannyl)acrylate (0.50 g, 1.2 mmol) in dry DMF (5 ml) with CuI (0.10 g, 0.5 mmol) and $Pd(PPh_3)_4$ (0.05 g, 0.043 mmol) gave 0.18 g (76%) of ester **3**, 97% purity. ^{19}F NMR ($CDCl_3$): –142.2 (dd, $^3J_{FF}$ = 119.5, $^3J_{FH}$ = 24.1, 1 F, F^1); –163.6 (dd, $^3J_{FF}$ = 119.5, $^4J_{FH}$ = 3.8, 1 F, F^2). ^1H NMR ($CDCl_3$): 7.35–7.53 (m, aromatic hydrogens, 5 H); 7.09 (d, $^3J_{HH}$ = 16.2, 1 H, H^g); 6.85 (ddd, $^3J_{HF}$ = 24.0, $^3J_{HH}$ = 16.1, $^4J_{HF}$ = 4.4, 1 H, H^f); 4.36 (q, $^3J_{HH}$ = 7.2, 2 H, H^b); 1.37 (t, $^3J_{HH}$ = 7.1, 3 H, H^a). ^{13}C NMR ($CDCl_3$): 159.9 (dd, $^2J_{CF}$ = 29.7, $^3J_{CF}$ = 5.7, C^c); 155.9 (dd, $^1J_{CF}$ = 261.0, $^2J_{CF}$ = 42.4, C^d or C^e); 138.1 (dd, $^1J_{CF}$ = 245.3, $^2J_{CF}$ = 39.0, C^e or C^d); 135.8 (m, C^f or C^g); 134.9 (s, aromatic carbon); 129.8 (s, aromatic carbon); 128.9 (s, aromatic carbon); 127.7 (s, aromatic carbon); 113.2 (d, $^2J_{CF}$ = 7.7, C^g or C^f); 61.6 (s, C^b); 14.4 (s, C^a). GC-MS (EI, *m/z* (rel.%)): 238 (58) [M^+], 218 (7), 193 (12), 173 (79), 165 (100) [M^+ – CO_2Et], 145 (49), 133 (30), 115 (25). TLC: R_F 0.30 (hexanes–ethyl acetate, 95 : 5).

Ethyl (2Z,4E)-2,3-Difluoro-5-phenyl-2,4-pentadienoate (**4**)



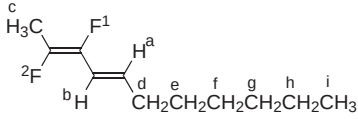
A $CDCl_3$ solution of ester **3** (0.19 g) in an NMR tube was treated with a few crystals of iodine. The isomerization process was monitored by ^{19}F NMR analysis of the above solution. After 7 days at room temperature (isomerization was static) the mixture was purified by silica gel chromatography to give 0.14 g (74%) of a mixture of ester **4** and the 2*E*,4*E*-isomer in a ratio of 85 : 15. ^{19}F NMR ($CDCl_3$): –127.6 (dd, $^3J_{FH}$ = 26.7, $^4J_{FH}$ = 2.6, 1 F, F^1); –150.8 (s, F^2). ^1H NMR ($CDCl_3$): 7.60 (ddd, $^3J_{HF}$ = 26.7, $^3J_{HH}$ = 16.1, $^4J_{HF}$ = 1.5, 1 H, H^f); 7.35–7.53 (m, aromatic hydrogens, 5 H); 7.21 (d, $^3J_{HH}$ = 16.3, 1 H, H^g); 4.36 (q, $^3J_{HH}$ = 7.2, 2 H, H^b); 1.39 (t, $^3J_{HH}$ = 7.2, 3 H, H^a). ^{13}C NMR ($CDCl_3$): 160.9 (dd, $^2J_{CF}$ = 26.8, $^3J_{CF}$ = 9.1, C^c); 154.7 (dd, $^1J_{CF}$ = 252.5, $^2J_{CF}$ = 16.4, C^d or C^e); 136.6 (dd, $^1J_{CF}$ = 261.2, $^2J_{CF}$ = 20.1, C^e or C^d); 136.1 (dd, $^2J_{CF}$ = 22.4, 6.3, C^f or C^g); 135.3 (s, aromatic carbon); 129.6 (s, aromatic carbon); 128.9 (s, aromatic carbon); 127.7 (d, J_{CF} = 1.2, aromatic carbon); 115.1 (dd, $^2J_{CF}$ = 15.5, $^3J_{CF}$ = 3.3, C^g or C^f); 61.8 (s, C^b); 14.1 (s, C^a). GC-MS (EI, *m/z* (rel.%)): 238 (46) [M^+], 218 (5), 193 (12), 173 (76), 165 (100) [M^+ – CO_2Et], 145 (51), 133 (32), 115 (25). TLC: R_F 0.30 (hexanes–ethyl acetate, 95 : 5).

(2E,4Z)-2,3-Difluoro-2,4-undecadiene (**5**)



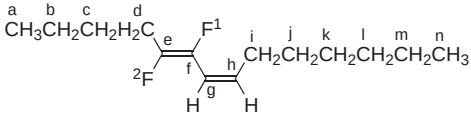
Similarly, the reaction of (*Z*)-1-iodo-1-octene (0.25 g, l.0 mmol) with (*Z*)-1,2-difluoro-1-tributylstannyl-1-propene (0.44 g, 1.2 mmol) in dry DMF (5 ml) with CuI (0.10 g, 0.5 mmol) and $Pd(PPh_3)_4$ (0.05 g, 0.043 mmol) gave 0.12 g (64%) of diene **5**. ^{19}F NMR ($CDCl_3$): –158.5 (ddd, $^3J_{FF}$ = 120.8, $^3J_{FH}$ = 31.8, $^4J_{FH}$ = 5.1, 1 F, F^1); –139.8 (dqd, $^3J_{FF}$ = 120.8, $^3J_{FH}$ = 16.5, $^4J_{FH}$ = 3.8, 1 F, F^2). ^1H NMR ($CDCl_3$): 5.98 (dddq, $^3J_{HF}$ = 31.5, $^3J_{HH}$ = 12.1, $^4J_{HF}$ = 4.7, $^5J_{HH}$ = 0.6, 1 H, H^d); 5.46 (dt, $^3J_{HH}$ = 12.0, 7.7, 1 H, H^e); 2.30 (q, $^3J_{HH}$ = 7.2, 2 H, H^f); 2.0 (dd, $^3J_{HF}$ = 17.3, $^4J_{HF}$ = 5.2, 3 H, H^a); 1.23–1.44 (m, 8 H, H^g–H^j); 0.85 (m, 3 H, H^k). ^{13}C NMR ($CDCl_3$): 148.6 (dd, $^1J_{CF}$ = 232.3, $^2J_{CF}$ = 44.6, C^b or C^c); 148.3 (dd, $^1J_{CF}$ = 244.2, $^2J_{CF}$ = 53.7, C^c or C^b); 132.7 (t, $^3J_{CF}$ = 3.7, C^e); 113.7 (d, $^2J_{CF}$ = 18.3, C^d); 31.7 (s); 29.8 (s); 29.1 (d, J_{CF} = 6.7, C^f); 28.9 (s); 22.6 (s); 14.1 (s, C^k); 12.5 (d, $^2J_{CF}$ = 25.0, C^a). GC-MS (EI, *m/z* (rel.%)): 188 (14) [M^+], 117 (5), 105 (6), 104 (100) [$M^+ - C_6H_{12}$), 95 (4), 77 (11), 65 (6), 55 (7).

(2E,4E)-2,3-Difluoro-2,4-undecadiene (**6**)



Similarly, the reaction of (*E*)-1-iodo-1-octene (0.24 g, 1.0 mmol) with (*Z*)-1,2-difluoro-1-tributylstannyl-1-propene (0.44 g, 1.2 mmol) in the presence of DMF (5 ml), CuI (0.10 g, 0.5 mmol) and Pd $(PPh_3)_4$ (0.05 g, 0.043 mmol) gave the (2*E*,4*E*) isomer **6** in 90% ^{19}F NMR yield (*vs* $C_6H_5CF_3$). The homo-coupled product could not be completely separated by silica gel chromatography. ^{19}F NMR ($CDCl_3$): –165.2 (ddq, $^3J_{FF}$ = 117.0, $^3J_{FH}$ = 28.0, $^4J_{FH}$ = 5.1, 1 F, F^1); –144.9 (dqd, $^3J_{FF}$ = 117.0, $^3J_{FH}$ = 17.8, $^4J_{FH}$ = 2.5, 1 F, F^2). ^1H NMR ($CDCl_3$): 6.19 (dddm, $^3J_{HF}$ = 27.2, $^3J_{HH}$ = 15.8, $^4J_{HF}$ = 4.0, 1 H, H^b); 5.87 (dt, $^3J_{HH}$ = 15.8, 7.0, 1 H, H^a); 2.13 (q, $^3J_{HH}$ = 6.9, 2 H, H^d); 2.03 (dd, $^3J_{HF}$ = 17.4, $^4J_{HF}$ = 4.9, 3 H, H^c); 1.28–1.44 (m, 8 H, H^e–H^h); 0.88 (m, 3 H, H^i). GC-MS (EI, *m/z* (rel.%)): 188 (12) [M^+], 117 (8), 105 (7), 104 (100) [$M^+ - C_6H_{12}$], 95 (5), 77 (16), 65 (9), 55 (10).

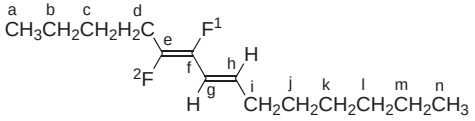
(5E,7Z)-5,6-Difluoro-5,7-tetradecadiene (**7**)



Similarly, the reaction of (*Z*)-1-iodo-1-octene (0.24 g, 1.0 mmol) with (*Z*)-1,2-difluoro-1-tributylstannyl-1-hexene (0.49 g, 1.2 mmol) in dry DMF (5 ml) with CuI (0.10 g, 0.5 mmol) and $Pd(PPh_3)_4$ (0.05 g, 0.043 mmol) gave 0.20 g (87%) of diene **7**. ^{19}F NMR

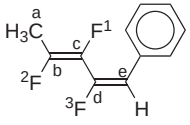
($CDCl_3$): –146.8 (dtd, $^3J_{FF}$ = 119.5, $^3J_{FH}$ = 24.2, $^4J_{FH}$ = 4.8, 1 F, F^2); –159.0 (dd, $^3J_{FF}$ = 119.7, $^3J_{FH}$ = 31.8, 1 F, F^1). ^1H NMR ($CDCl_3$): 5.98 (dddt, $^3J_{HF}$ = 32.3, $^3J_{HH}$ = 12.1, $^4J_{HF}$ = 4.7, $^4J_{HH}$ = 1.6, 1 H, H^g); 5.47 (dtd, $^3J_{HH}$ = 12.0, 7.7, $^4J_{HF}$ = 1.3, 1 H, H^h); 2.27–2.46 (m, 4 H, H^d and H^i); 1.27–1.58 (m, 12 H, H^b, H^c, H^j, H^k, H^l, H^m); 0.85–0.95 (m, 6 H, H^a and H^n). ^{13}C NMR ($CDCl_3$): 151.6 (dd, $^1J_{CF}$ = 246.6, $^2J_{CF}$ = 53.1, C^e or C^f); 148.4 (dd, $^1J_{CF}$ = 232.5, $^2J_{CF}$ = 45.2, C^g or C^h); 132.8 (m, C^f or C^g); 113.9 (d, $^2J_{CF}$ =18.3, C^g or C^h); 31.7 (s); 29.8 (s); 29.2 (d, J_{CF} = 6.7); 28.9 (s); 27.9 (s); 26.1 (d, $^2J_{CF}$ = 23.8, C^d); 22.6 (s); 22.1 (s); 14.0 (s); 13.67 (s). GC-MS (EI, *m/z* (rel.%)): 230 (28) [M^+], 159 (7), 146 (100) [$M^+ - C_6H_{12}$], 131 (12), 115 (25), 103 (54).

(5E,7E)-5,6-Difluoro-5,7-tetradecadiene (**8**)



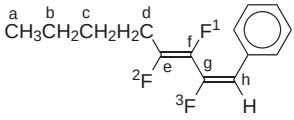
Similarly, the reaction of (*E*)-1-iodo-1-octene (0.24 g, 1.0 mmol) with (*Z*)-1,2-difluoro-1-tributylstannyl-1-hexene (0.49 g, 1.2 mmol) in the presence of DMF (5 ml), CuI (0.10 g, 0.5 mmol) and $Pd(PPh_3)_4$ (0.05 g, 0.043 mmol) gave the (5*E*,7*E*) isomer **8** in 90% ^{19}F NMR yield (*vs* $C_6H_5CF_3$). The homo-coupled product could not be completely separated by silica gel chromatography. ^{19}F NMR ($CDCl_3$): –151.9 (dtd, $^3J_{FF}$ = 116.9, $^3J_{FH}$ = 22.9, $^4J_{FH}$ = 2.6, 1 F, F^2); –165.7 (ddt, $^3J_{FF}$ = 116.9, $^3J_{FH}$ = 26.7, $^4J_{FH}$ = 5.1, 1 F, F^1). ^1H NMR ($CDCl_3$): 6.18 (dddt, $^3J_{FF}$ = 27.1, $^3J_{HH}$ = 15.8, $^4J_{HF}$ = 4.0, $^4J_{HH}$ = 1.5, 1 H, H^2); 6.50 (dt, $^3J_{HH}$ = 14.3, 7.5, 1 H, H^h). GC-MS (EI, *m/z* (rel.%)): 230 (36) [M^+], 159 (11), 146 (100) [$M^+ - C_6H_{12}$], 131 (12), 115 (22), 103 (43).

(1E,3E)-2,3,4-Trifluoro-1-phenyl-1,3-pentadiene (**9**)



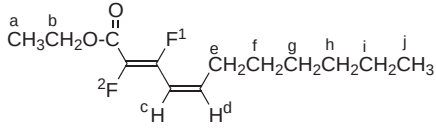
Similarly, the reaction of (*Z*)-β-bromo-β-fluorostyrene (0.20 g, 1.0 mmol) with (*Z*)-1,2-difluoro-1-tributylstannyl-1-propene (0.44 g, 1.2 mmol) in dry DMF (5 ml) with CuI (0.10 g, 0.5 mmol) and $Pd(PPh_3)_4$ (0.05 g, 0.043 mmol) gave 0.15 g (76%) of diene **9**; GLPC > 98%. ^{19}F NMR ($CDCl_3$): –111.9 (dddq, $^3J_{FF}$ = 36.9, $^3J_{FH}$ = 19.0, $^4J_{FF}$ = 15.3, $^5J_{FH}$ = 3.8, 1 F, F^3); –129.4 (dqd, $^3J_{FF}$ = 131.0, $^3J_{FH}$ = 16.8, $^4J_{FF}$ = 15.3, 1 F, F^2); –162.7 (ddq, $^3J_{FF}$ = 131.0, 36.9, $^4J_{FH}$ = 5.7, 1 F, F^1). ^1H NMR ($CDCl_3$): 7.27 (m, aromatic hydrogens, 5 H); 6.55 (d, $^3J_{HF}$ = 18.8, 1 H, H^e); 2.04 (ddd, $^3J_{HF}$ = 17.1, $^4J_{HF}$ = 5.3, $^5J_{HF}$ = 4.0, 3 H, H^a). ^{13}C NMR ($CDCl_3$): 152.1 (ddd, $^1J_{CF}$ = 253.0, $^2J_{CF}$ = 52.1, $^3J_{CF}$ = 4.2, C^b or C^d); 146.8 (ddd, $^1J_{CF}$ = 244.1, $^2J_{CF}$ = 27.4, $^3J_{CF}$ = 4.3, C^b or C^d); 141.0 (ddd, $^1J_{CF}$ = 227.0, $^2J_{CF}$ = 49.4, 33.6, C^c); 132.0 (d, J_{CF} = 10.3, aromatic carbon); 128.4 (s, aromatic carbon); 128.0 (d, J_{CF} = 19.5, aromatic carbons, two overlapping peaks); 115.8 (dt, $^2J_{CF}$ = 28.7, $^4J_{CF}$ = 3.1, C^e); 13.1 (d, $^2J_{CF}$ = 24.4, C^a). GC-MS (EI, *m/z* (rel.%)): 198 (87) [M^+], 183 (100) [$M^+ - CH_3$], 177 (48), 164 (31), 151 (32), 133 (80), 129 (11).

(1E,3E)-2,3,4-Trifluoro-1-phenyl-1,3-octadiene (**10**)



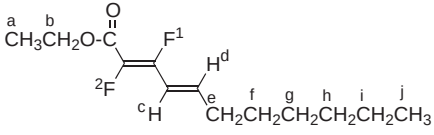
Similarly, the reaction of (*Z*)-β-bromo-β-fluorostyrene (0.20 g, 1.0 mmol) with (*Z*)-1,2-difluoro-1-tributylstannyl-1-hexene (0.48 g, 1.2 mmol) in dry DMF (4 ml) with CuI (0.10 g, 0.5 mmol) and $Pd(PPh_3)_4$ (0.05 g, 0.043 mmol) gave 0.17 g (71%) of diene **10**; GLPC > 98%. ^{19}F NMR ($CDCl_3$): –111.5 (m, 1 F, F^3); –136.1 (dtd, $^3J_{FF}$ = 131.0, $^3J_{FH}$ = 22.9, $^4J_{FF}$ = 14.0, 1 F, F^2); –163.3 (dd, $^3J_{FF}$ = 131.0, 36.8, 1 F, F^1). ^1H NMR ($CDCl_3$): 7.20–7.31 (m, aromatic hydrogens, 5 H); 6.54 (d, $^3J_{HF}$ = 18.6, 1 H, H^h); 2.23–2.46 (m, 2 H, H^d); 1.25–1.53 (m, 4 H, H^b and H^c); 0.90 (t, *J* = 7.2, 3 H, H^a). ^{13}C NMR ($CDCl_3$): 155.2 (ddd, $^1J_{CF}$ = 255.5, $^2J_{CF}$ = 51.2, $^3J_{CF}$ = 4.9, C^e or C^g); 147.1 (ddd, $^1J_{CF}$ = 244.7, $^2J_{CF}$ = 27.5, $^3J_{CF}$ = 4.9, C^e or C^g); 140.7 (ddd, $^1J_{CF}$ = 227.1, $^2J_{CF}$ = 50.4, 33.3, C^f); 132.1 (d, J_{CF} = 10.0, aromatic carbon); 128.4 (s, aromatic carbon); 128.2 (s, aromatic carbon); 127.9 (s, aromatic carbon); 115.9 (dt, $^2J_{CF}$ = 28.7, $^3J_{CF}$ = 3.1, C^h); 27.1 (s, C^c); 26.6 (d, $^2J_{CF}$ = 22.6, C^d); 22.0 (s, C^b); 13.6 (s, C^a). GC-MS (EI, *m/z* (rel.%)): 240 (38) [M^+], 194 (24), 183 (100) [$M^+ - C_4H_9$], 177 (64), 164 (29), 157 (10), 146 (38), 133 (25), 127 (11).

Ethyl (2E,4Z)-2,3-Difluoro-2,4-undecadienoate (**11**)



Similarly, the reaction of (*Z*)-1-iodo-1-octene (0.24 g, 1.0 mmol) with ethyl (*Z*)-2,3-difluoro-3-(tributylstannyl)acrylate (0.50 g, 1.2 mmol) in the presence of DMF (5 ml), CuI (0.10 g, 0.5 mmol) and $Pd(PPh_3)_4$ (0.05 g, 0.043 mmol) gave the (2*E*,4*Z*) isomer **11** in 91% ^{19}F NMR yield (*vs* $C_6H_5CF_3$). The homo-coupled product could not be completely separated by silica gel chromatography. ^{19}F NMR ($CDCl_3$): –134.4 (dd, $^3J_{FF}$ = 124.6, $^3J_{FH}$ = 30.5, 1 F, F^1); –161.8 (dd, $^3J_{FF}$ = 123.3, $^4J_{FH}$ = 3.8, 1 F, F^2). ^1H NMR ($CDCl_3$): 6.05 (dddt, $^3J_{HF}$ = 30.6, $^3J_{HH}$ = 12.1, $^4J_{HF}$ = 5.1, $^4J_{HH}$ = 1.5, 1 H, H^c); 5.89 (dtd, $^3J_{HH}$ = 12.0, 7.4, $^4J_{HF}$ = 1.6, 1 H, H^d). GC-MS (EI, *m/z* (rel.%)): 246 (3) [M^+], 201 (4), 178 (5), 163 (9), 134 (100) [$M^+ - C_6H_{12} - C_2H_4$], 117 (10), 97 (12).

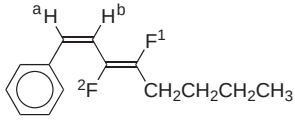
Ethyl (2E,4E)-2,3-Difluoro-2,4-undecadienoate (**12**)



Similarly, the reaction of (*E*)-1-iodo-1-octene (0.24 g, 1.0 mmol) with ethyl (*Z*)-2,3-difluoro-3-(tributylstannyl)acrylate (0.5 g, 1.2 mmol) in the presence of DMF (5 ml), CuI (0.10 g, 0.5 mmol) and $Pd(PPh_3)_4$ (0.05 g, 0.043 mmol) gave the (2*E*,4*E*) of isomer **12** in 90%

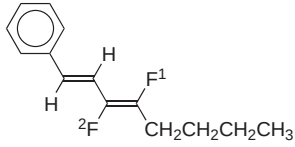
^{19}F NMR yield (*vs* $C_6H_5CF_3$). The homo-coupled product could not be completely separated by silica gel chromatography. ^{19}F NMR ($CDCl_3$): –141.2 (dd, $^3J_{FF}$ = 122.1, $^3J_{FH}$ = 24.2, 1 F, F^1); –166.7 (dd, $^3J_{FF}$ = 122.0, $^4J_{FH}$ = 3.2, 1 F, F^2). ^1H NMR ($CDCl_3$): 6.32–6.43 (m, 1 H, H^d); 6.22 (dddt, $^3J_{HF}$ = 24.2, $^3J_{HH}$ = 15.8, $^4J_{HF}$ = 4.3, $^4J_{HH}$ = 1.4, 1 H, H^c). GC-MS (EI, *m/z* (rel.%)): 246 (4) [M^+], 201 (4), 178 (4), 153 (6), 134 (100) [$M^+ - C_6H_{12} - C_2H_4$], 97 (16).

(1Z,3E)-3,4-Difluoro-1-phenyl-1,3-octadiene (**13**)



Similarly, the reaction of (*Z*)-β-iodostyrene (0.23 g, 1.0 mmol) with (*Z*)-1,2-difluoro-1-tributylstannyl-1-hexene (0.49 g, 1.2 mmol) in the presence of DMF (5 ml), CuI (0.10 g, 0.5 mmol) and $Ph(PPh_3)_4$ (0.05 g, 0.043 mmol) gave the (1*Z*,3*E*) isomer of **13** in 93% ^{19}F NMR yield (*vs* $C_6H_5CF_3$). The homo-coupled product could not be completely separated by silica gel chromatography. ^{19}F NMR ($CDCl_3$): –142.7 (dtd, $^3J_{FF}$ = 119.6, $^3J_{FH}$ = 22.9, $^4J_{FH}$ = 2.0, 1 F, F^1); –154.9 (dd, $^3J_{FF}$ = 119.5, $^3J_{FH}$ = 30.6, 1 F, F^2). ^1H NMR ($CDCl_3$): 6.47 (dd, $^3J_{HH}$ = 12.8, $^4J_{HF}$ = 0.3, 1 H, H^a); 6.24 (ddd, $^3J_{HF}$ = 30.5, $^3J_{HH}$ = 12.7, $^4J_{HF}$ = 4.9, 1 H, H^b). GC-MS (EI, *m/z* (rel.%)): 222 (49) [M^+], 179 (56), 159 (100) [$M^+ - C_3H_7 - HF$], 146 (42), 133 (46), 128 (34), 101 (18).

(1E,3E)-3,4-Difluoro-1-phenyl-1,3-octadiene (**14**)



Similarly, the reaction of (*E*)-β-iodostyrene (0.23 g, 1.0 mmol) with (*Z*)-1,2-difluoro-1-tributylstannyl-1-hexene (0.49 g, 1.2 mmol) in the presence of DMF (5 ml), CuI (0.10 g, 0.5 mmol) and $Pd(PPh_3)_4$ (0.05 g, 0.043 mmol) gave the (1*E*,3*E*) isomer of **14** in 91% ^{19}F NMR yield (*vs* $C_6H_5CF_3$). The homo-coupled product could not be easily separated by silica gel chromatography. ^{19}F NMR ($CDCl_3$): –147.3 (dtd, $^3J_{FF}$ = 115.7, $^3J_{FH}$ = 22.9, $^4J_{FH}$ = 3.8, 1 F, F^1); –165.5 (ddt, $^3J_{FF}$ = 115.7, $^3J_{FH}$ = 25.4, $^4J_{FH}$ = 3.8, 1 F, F^2). GC-MS (EI, *m/z* (rel.%)): 222 [M^+] detected.

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