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Journal of Fluorine Chemistry 128 (2007) 71–77
JOURNAL OF FLUORINE CHEMISTRY
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Stereospecific preparation of symmetrical (1*Z*, 3*Z*)- and (1*E*, 3*E*)-2,3-difluoro-1,4-disubstituted-buta-1,3-dienes from 1-bromo-1-fluoroalkenes

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Received 16 August 2006; accepted 3 October 2006
Available online 10 October 2006

Abstract

A straightforward method to prepare symmetrical (1*Z*, 3*Z*)- and (1*E*, 3*E*)-2,3-difluoro-1,4-disubstituted-buta-1,3-dienes is described. High *E*/*Z* ratio 1-bromo-1-fluoroalkenes, prepared by isomerization from the *E*/*Z* ≈ 1:1 isomeric mixtures, reacted with $Bu_3SnSnBu_3$ and $Pd(PPh_3)_4$ to afford (1*Z*, 3*Z*)-2,3-difluoro-1,4-disubstituted-buta-1,3-dienes in good yield. (*Z*)-1-Bromo-1-fluoroalkenes, which were prepared by kinetic reduction from 1-bromo-1-fluoroalkenes (*E*/*Z* ≈ 1:1), can undergo similar reaction with $Bu_3SnSnBu_3$ and $Pd(PPh_3)_4$/CuI to prepare (1*E*, 3*E*)-2,3-difluoro-1,4-disubstituted-buta-1,3-dienes.

Keywords: Fluorodiene; Palladium-catalyzed cross-coupling; Stereospecific; Bromofluoroalkenes; Bis(tributyltin)

1. Introduction

Fluoroorganic compounds continue to be of strong interest in polymer chemistry, medicinal chemistry and agrochemistry because of the unique properties these compounds exhibited when fluorine atoms are strategically placed in the molecule [1–3]. As conjugated dienes and polyenes widely exist as the essential feature of many natural products, such as pheromones and juvenile hormones [4], there is increased research interest in the synthesis and biological activity of their fluorinated analogues [5–11]. The reaction between Wittig reagents and α-fluoro-α,β-unsaturated aldehydes has been used to prepare fluorinated dienes, however the starting materials are difficult to prepare and the stereoselectivity is poor [5]. Popular methodologies for the preparation of fluorinated dienes include: palladium/copper(I) halide catalyzed coupling reactions between vinylstannanes and vinyl halides [12–14]; the coupling reaction between fluorinated vinyl zinc reagent and vinyl halides [15–18]; the coupling reaction between fluorinated vinyl copper reagent with vinyl halides [19] and copper(II) salts-mediated homo-coupling of 1,2-difluorovinylstannanes [20]. However few synthetic methods are available for the preparation of symmetrical fluorinated dienes: McCarthy and co-workers have reported symmetrical fluorinated dienes from palladium-catalyzed coupling reactions between (α-fluoro) vinyl stannanes and phenyl triflate, oxalyl chloride, and ethyl chloroformate [21,22]. Wnuk and co-workers also obtained symmetrical fluorinated dienes in the palladium-catalyzed coupling reactions between (α-fluoro) vinyl tris(trimethylsilyl)germanes and aryl or alkenyl halides [23]; recently Rolando and co-workers reported the synthesis of (1*E*, 3*E*)-2,3-difluoro-1,4-disubstituted-buta-1,3-dienes from (*Z*)-1-bromo-1-fluoroalkenes in the presence of bis(pinacolato)diborane and $Cl_2Pd(PPh_3)_2$ [24]. Herein, we detail the preparation of both (1*Z*, 3*Z*)- and (1*E*, 3*E*)-2,3-difluoro-1,4-disubstituted-buta-1,3-dienes via the $Pd(PPh_3)_4$/$Bu_3SnSnBu_3$-mediated homo-coupling of 1-bromo-1-fluoroalkenes. A portion of this work has appeared in a preliminary communication [25].

2. Results and discussion

2.1. Preparation of symmetrical (1*Z*, 3*Z*)-2,3-difluoro-1,4-disubstituted-buta-1,3-dienes

1-Bromo-1-fluoroalkenes **1** (*E*/*Z* ≈ 1:1) can be readily prepared by established methods [26–28], and are useful synthons for the preparation of a variety of fluorinated organic compounds [29–31]. Recently we reported that **1** can isomerize

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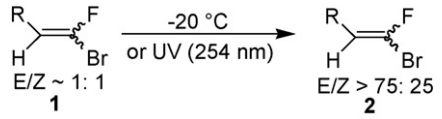
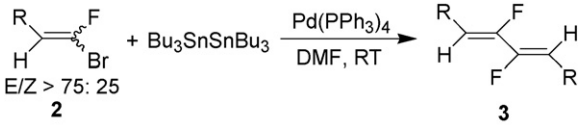
doi:10.1016/j.jfluchem.2006.10.002



Scheme 1.



Scheme 2.

to high *E*/*Z* ratios [29,32]; for **1** (R = aryl groups), high *E*/*Z* ratios (*E*/*Z* > 75:25) were obtained after storage in a freezer (−20 °C) for 1 week (Scheme 1). Alternatively, the isomerization readily occurs when **1** undergoes photolysis at 254 nm for approximately 1 h. The isomerization is very clean and is most likely due to a trace amount of bromine in the mixture. However, for those **1** (R = 1-naphthyl or alkyl groups), no obvious isomerization was detected (Scheme 2).

Recently we reported that the (*E*) isomer of **1** reacts faster than the corresponding (*Z*) isomer at room temperature in palladium-catalyzed coupling reaction [33,34]. It has also been demonstrated that the reactivity difference occurred in the first step of oxidative addition between Pd(0) catalyst and **1** [33]. In an effort to prepare (*E*)-1-fluoro-2-phenylvinyl tributyltin, which is a useful synthon [21,22], we tested the coupling reaction between high *E*/*Z* ratio 1-bromo-1-fluoroalkenes **2** and $Bu_3SnSnBu_3$ with $Pd(PPh_3)_4$ as the catalyst [35,36]. Thus 1-bromo-1-fluoro-2-phenylethene (*E*/*Z* = 85:15), **2a**, was reacted with $Bu_3SnSnBu_3$ and $Pd(PPh_3)_4$ (4 mol%) in THF at room temperature. Surprisingly, rather than formation of (*Z*)-1-fluoro-2-phenylvinyltributyltin, the major product obtained was (1*Z*, 3*Z*)-2,3-difluoro-1,4-diphenyl-buta-1,3-diene **3a**. A trace amount of the (1*Z*, 3*E*) isomeric diene was also detected in the reaction mixture by ^{19}F NMR analysis. The desired (1*Z*, 3*Z*)-diene was successfully isolated from the reaction mixture by silica gel column chromatography, followed by recrystallization, and was characterized by ^{19}F, ^{1}H, ^{13}C NMR, GC–MS, and HRMS analysis. The yield was 64% (75% conversion based on the amount of the starting (*E*)-1-bromo-1-fluoroalkene).

McCarthy and co-workers had also observed similar symmetrical 2,3-difluoro-1,4-disubstituted-butadienes as a side product in the palladium-catalyzed coupling reaction between 1-fluorovinyltin and phenyl triflate, oxalyl chloride and ethyl chloroformate [21,22]. Although symmetrical biaryls have been occasionally reported in some palladium-catalyzed coupling reactions between aryl halides and $Bu_3SnSnBu_3$ [37–40], to the best of our knowledge, this type of homo-coupling reaction has not been previously reported as an effective method to prepare symmetrical fluorinated dienes.

Similar reactions between other high *E*/*Z* ratio 1-bromo-1-fluoroalkenes and $Bu_3SnSnBu_3$ catalyzed by $Pd(PPh_3)_4$ in DMF were also carried out. (1*Z*, 3*Z*)-Dienes were successfully formed and isolated in good yields (Table 1). For the starting materials of high *E*/*Z* ratio **2** (R = substituted aryl groups), various functional groups can be tolerated. For those **2** (R = alkyl groups), the coupling reactions still worked well and the corresponding (1*Z*, 3*Z*)-diene was isolated in good yield (Table 1, entry 7).

Table 1
Preparation of symmetrical dienes **3** from **2**

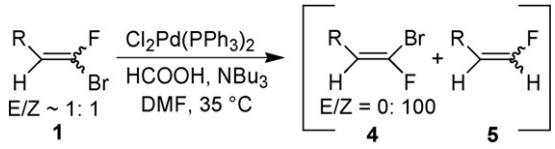
Entry	R of **2**	*E*/*Z* of **2**	Time (h)	Isolated yield (%)[a]
1	Ph, **2a**	85:15	68	64 (75)[b] **3a**
2	*o*-ClC_6H_4, **2b**	82:18	45	71 (86) **3b**
3	*p*-$MeOC_6H_4$, **2c**	81:19	40	43 (53) **3c**
4	*p*-ClC_6H_4, **2d**	88:12	41	72 (82) **3d**
5	*p*-FC_6H_4, **2e**	87:13	53	72 (83) **3e**
6	*m*-$NO_2C_6H_4$, **2f**	81:19	130	54 (66) **3f**
7	$PhC(CH_3)H$, **2g**	83:17[c]	46	67 (81) **3g**

[a] All products gave satisfactory ^{19}F, ^{1}H, ^{13}C, GC–MS and HRMS data; the number in the parenthesis is the conversion that was calculated based on the amount of the starting (*E*) isomer in **2**.
[b] Reaction was carried out in THF instead of DMF.
[c] This *E*/*Z* ratio was achieved after partial separation of *E*/*Z* ~ 1:1 mixture via column chromatography.

For one of the substrates (R = *p*-$MeOC_6H_4$), the yield of **3c** is obviously lower than the other reported examples. This lower yield is due to the formation of a considerable amount of the (1*Z*, 3*E*) isomeric diene, as observed by ^{19}F NMR analysis of the reaction mixture. There are two possibilities for the formation of this (1*Z*, 3*E*)-diene: it could be formed in the coupling reaction, or alternatively, the desired (1*Z*, 3*Z*)-diene that was formed by the coupling reaction could isomerize to the corresponding (1*Z*, 3*E*)-diene. An exploratory experiment was designed to test these two possibilities. A small amount of pure (1*Z*, 3*Z*)-diene **3c** was dissolved in DMF in a NMR tube. ^{19}F NMR analysis showed no isomerization in two days. When two drops of $Bu_3SnSnBu_3$ were added to the solution in the NMR tube, we noticed that approximately 20% of the (1*Z*, 3*Z*)-diene isomerized to the (1*Z*, 3*E*)-diene in 12 h. More (1*Z*, 3*E*)-diene was observed after a longer time before the mixture reached equilibrium. It is likely that this particular (1*Z*, 3*E*)-diene was formed by isomerization from the corresponding (1*Z*, 3*Z*)-diene. This isomerization could be initiated by trace amount of tributyltin radical, which is formed when bis(tributyltin) is exposed to UV light in a typical laboratory environment. It seems that dienes or ethenes that bear the *p*-$MeOC_6H_4$– group have an obvious tendency to readily isomerize. For example, the similar diene (1*E*, 3*E*)-*p*-$MeOC_6H_4CF{=}CFCF{=}CFCF_6H_4OMe$-*p* easily isomerized at room temperature [20]; (*E*)-*p*-$MeOC_6H_4CF{=}CFC_6H_4OMe$-*p* was also readily isomerized to an (*E*), (*Z*) isomeric mixture when irradiated with UV light [41].

2.2. Preparation of (1E, 3E)-2,3-difluoro-1,4-disubstituted-buta-1,3-dienes

It has been demonstrated that at higher temperature [33] or over a longer reaction time [34] (*Z*)-1-bromo-1-fluoroalkenes **4** can undergo similar coupling reactions as the (*E*) isomers at room temperature. Following the preparation of (1*Z*, 3*Z*)-2,



Scheme 3.

3-difluoro-1,4-disubstituted-buta-1,3-dienes, the synthesis of symmetrical (1*E*, 3*E*) isomeric dienes from **4** was investigated by the same method. Recently, we reported the preparation of (*Z*)-1-bromo-1-fluoroalkenes by kinetic reduction of **1** (Scheme 3) [32]. (*Z*)-1-Bromo-1-fluoroalkenes **4** can be obtained in pure form, however most of them were utilized with the corresponding reduced products **5** in a mixture to avoid tedious isolation and to improve the overall yield [29–32]. Therefore (*Z*)-1-bromo-1-fluoro-2-phenylethene **4a** was reacted with $Bu_3SnSnBu_3$ (1.2 equiv.), $Pd(PPh_3)_4$ (4 mol%) at 70 °C and the reaction progress was monitored by ^{19}F NMR. (1*E*, 3*E*)-2,3-Difluoro-1,4-diphenyl-buta-1,3-diene **6a** was formed as the major product but considerable amount of (1*Z*, 3*E*) and (1*Z*, 3*Z*) isomeric dienes **7**, **3a** were also detected (Scheme 4). The desired (1*E*, 3*E*)-diene **6a** could not be separated from **7** and **3a** by silica gel column chromatography.

However, we discovered that the (1*E*, 3*E*)-dienes could be formed as the only product at room temperature with the addition of 0.5 equiv. of CuI as co-catalyst to the mixture (Scheme 5). For example, when the mixture of (*Z*)-1-bromo-1-fluoro-2-(2-chlorophenyl)-ethene **4b** and the reduced products was reacted with $Bu_3SnSnBu_3$ (1.2 equiv.), $Pd(PPh_3)_4$ (4 mol%), CuI (0.5 equiv.) in DMF at room temperature, ^{19}F NMR analysis of the reaction mixture showed that only the (1*E*, 3*E*)-diene **6b** was formed and the reduced products did not participate in the reaction. Pure product (**6b**) was successfully isolated by silica gel column chromatography followed by recrystallization. The yield was 88% (Table 2). Similar methodology also worked for other (*Z*)-1-bromo-1-fluoroalkenes, such as **4a** and **4c**. In certain cases, the preparation of similar symmetrical (1*E*, 3*E*)-dienes was unsuccessful however. For example, when R = 1-naphthyl, the reaction between (*Z*)-1-bromo-1-fluoroalkene (in a mixture with the corresponding reduced products) and bistributyltin was carried out at 40 °C (the reaction was very slow at room temperature). ^{19}F NMR analysis of the reaction mixture showed that the desired (1*E*, 3*E*)-diene was formed as the only product. However, this product could not be isolated pure due to its obvious isomerization tendency in the course of separation. When R = $PhCHCH_3$ and *n*-C_7H_{15}, (*Z*)-1-bromo-1-fluoroalkenes **4** (in a mixture with the corresponding reduced products **5**) and $Bu_3SnSnBu_3$/CuI/DMF did not react at room temperature; at higher temperatures the reactions were still sluggish even at longer reaction times; the separation of pure products from these reactions mixtures failed.

Table 2
Preparation of symmetrical (1*E*, 3*E*)-2,3-difluoro-buta-1,3-dienes from (*Z*)-1-bromo-1-fluoroalkenes

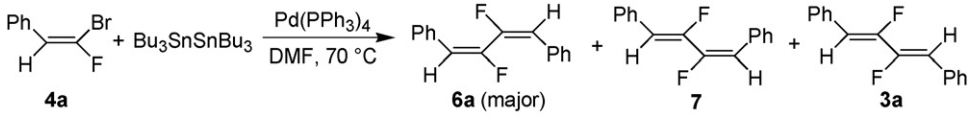
Entry	R of **4**	*E*/*Z* of **4**	Temp (°C)	Time (h)	Isolated yield (%)
1	Ph, **4a**	0:100	RT	39	93[a] **6a**
2	*o*-ClC_6H_4, **4b**	0:100	RT	44	88[b] **6b**
3	*p*-$MeOC_6H_4$, **4c**	0:100	RT	20	53[c] **6c**

[a] 10 mol% $Pd(PPh_3)_4$, 1.0 equiv. CuI were used.
[b] 4 mol% $Pd(PPh_3)_4$, 0.5 equiv. CuI were used.
[c] 10 mol% $Pd(PPh_3)_4$, 1.25 equiv. CuI were used; the product contains 6% impurity which could not be separated.

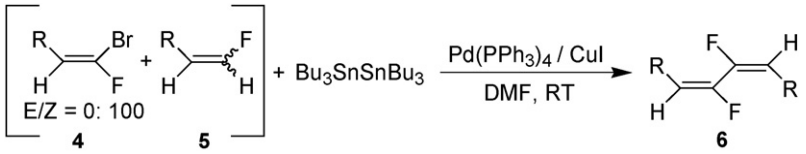
2.3. Mechanism

It was found that in the absence of $Pd(PPh_3)_4$ the reaction between high *E*/*Z*-1-bromo-1-fluoroalkenes **2** and $Bu_3SnSnBu_3$ failed. In the reaction between **2** and $Bu_3SnSnBu_3$/$Pd(PPh_3)_4$ in DMF, trace amount of 1-fluorovinyltributyltin had been detected by ^{19}F NMR analysis when the reactions were in progress. Therefore it is reasonable to propose that 1-fluorovinytin serves as an intermediate. In the coupling reactions between aryl halides and Pd(0)/$Bu_3SnSnBu_3$ aryl stannanes had been similarly proposed to be the key intermediate [39].

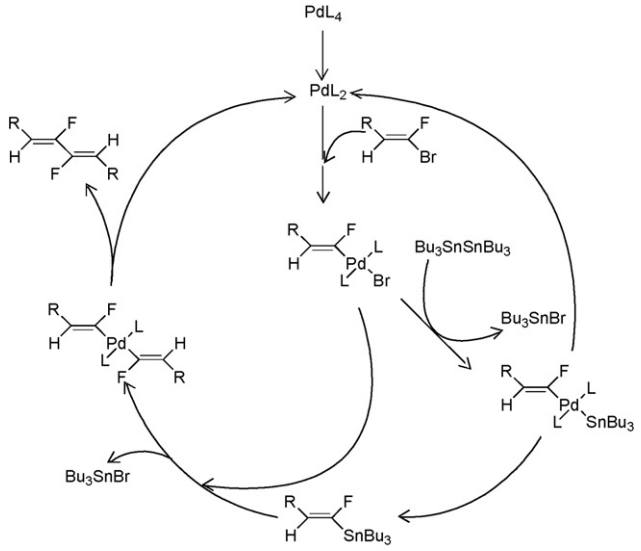
The proposed mechanism is shown in Scheme 6: L_4Pd (L = PPh_3) first loses two ligands to generate $L_2Pd(0)$, the active catalyst; the oxidative addition between $L_2Pd(0)$ and (*E*)-1-bromo-1-fluoroalkene leads to the vinyl palladium(II) bromide complex; this complex undergoes transmetallation with $Bu_3SnSnBu_3$ to form the vinyl palladium(II) tin



Scheme 4.



Scheme 5.



Scheme 6. Proposed mechanism for the formation of symmetrical (1*Z*, 3*Z*)-dienes.

intermediate; reductive elimination of this vinyl palladium(II) tin intermediate generates1-fluorovinyltin; transmetallation between the newly formed 1-fluorovinyltin and the vinyl palladium(II) bromide complex gives bis(vinyl) palladium(II) complex; finally symmetrical diene is formed by reductive elimination, and the active $L_2Pd(0)$ catalyst is recycled.

It has been shown that (*Z*)-1-bromo-1-fluoroalkenes can undergo oxidative addition at 70 °C or higher temperature [33]. The mechanism for the room temperature formation of (1*E*, 3*E*)-2,3-difluoro-buta-1,3-dienes from (*Z*)-1-bromo-1-fluoroalkenes in the presence of 0.5 equiv. of CuI is not very clear at this moment. CuI has been demonstrated to be a good cocatalyst in a variety of palladium-involved coupling reactions [12,21,42,43], it even makes the Sonogashira coupling reaction between (*Z*)-1-bromo-1-fluoroalkenes and terminal alkynes possible at room temperature [34]. In this Sonogashira coupling reaction, it is likely that CuI greatly accelerates the transmetallation step, which makes the first step of oxidative addition possible at room temperature. Similarly, in the room temperature formation of (1*E*, 3*E*)-2,3-difluoro-buta-1,3-dienes from (*Z*)-1-bromo-1-fluoroalkenes in the presence of CuI, it can be argued that CuI also accelerates the two transmetallation steps (from vinyl palladium(II) bromide to vinyl palladium tin, and from 1-flurovinytin to bis(vinyl)palladium(II) complex, respectively), therefore the oxidative addition between (*Z*)-1-bromo-1-fluoroalkene and $L_2Pd(0)$ becomes feasible at room temperature.

In conclusion, the readily available starting materials 1-bromo-1-fluoroalkenes were used as precursors for the preparation of symmetrical (1*Z*, 3*Z*)- and (1*E*, 3*E*)-2,3-difluoro-1,4-disubstituted-buta-1,3-dienes. Isomerization of 1-bromo-1-fluoroalkenes ($E/Z \approx 1{:}1$) can lead to high *E*/*Z* ratios ($E/Z > 75{:}25$) by storage at −20 °C or by photolysis at 254 nm. These high *E*/*Z* ratio 1-bromo-1-fluoroalkenes react with $Pd(PPh_3)_4$ and $Bu_3SnSnBu_3$ to afford symmetrical (1*Z*, 3*Z*)-dienes in good yields. (*Z*)-1-Bromo-1-fluoroalkenes, which were prepared by kinetic reduction of the $E/Z \approx 1{:}1$ isomeric mixtures, can undergo similar coupling reaction with $Pd(PPh_3)_4$, CuI and $Bu_3SnSnBu_3$ to provide the symmetrical (1*E*, 3*E*)-dienes.

3. Experimental

3.1. General experimental procedures

All reaction mixtures were monitored by ^{19}F NMR analysis using a Bruker AC-300. The ^1H, ^{19}F, ^{13}C spectra of the final products were obtained on a Bruker AC-300 ($CDCl_3$, $CFCl_3$ or TMS were used as the internal references, respectively). Low resolution mass spectra analyses were performed at 70 eV in the electron-impact mode on a single-quardrapole instrument interfaced to a gas chromatograph. High-resolution mass spectra (HRMS) were obtained in the University of Iowa High Resolution Mass Spectrometry Facility. Melting points were obtained in a Thomas-Hoover Unimelt apparatus and are uncorrected.

3.2. General procedures for the preparation of (1Z, 3Z)-dienes (**3**)

A 25 ml dry round-bottom flask equipped with a stirring bar and a N_2 tee, was charged with $Pd(PPh_3)_4$ (0.16 g, 0.14 mmol) and dry DMF (5 ml). High *E*/*Z* ratio 1-bromo-1-fluoroalkene (4.0 mmol, includes (*E*) isomer 3.4 mmol) was added and the solution was stirred at room temperature for 15 min. After the addition of $Bu_3SnSnBu_3$ (2.37 g, 4.08 mmol), the reaction mixture was allowed to stir at room temperature. When the reaction was completed, $Co(OAc)_2{\cdot}4H_2O$ (1.25 g, 5.0 mmol) was added to remove tributyltin halides from the reaction mixture [44]. Silica gel column chromatography followed by recrystallization provided pure products.

3.2.1. (1Z, 3Z)-2,3-Difluoro-1,4-diphenyl-butadiene (**3a**)

Similarly, a mixture of 1-bromo-1-fluoro-2-phenylethene (0.80 g, 4.0 mmol, $E/Z = 85{:}15$), bis(tributyltin) (2.37 g, 4.1 mmol), $Pd(PPh_3)_4$ (0.16 g, 0.14 mmol) in THF (8 ml) at room temperature for 68 h gave 0.31 g white crystals after a silica gel column (hexanes, $R_f = 0.27$) followed by recrystallization from hexanes. The 64% yield (75% conversion based on the consumed (*E*) 1-bromo-1-fluoroalkene). (1*Z*, 3*Z*) 100%. ^{19}F NMR ($CDCl_3$) (ppm): δ −128.4 (dd, $^3J_{FH(trans)} = 28.1$ Hz, $^4J_{FH} = 14.7$ Hz, 2F); ^1H NMR ($CDCl_3$) (ppm): δ 7.60 (d, $J = 7.4$ Hz, 4H), 7.38 (tm, $J = 7.6$ Hz, 4H), 7.29 (tm, $J = 7.4$ Hz, 2H), 6.24 (dd, $^3J_{HF(trans)} = 28.7$ Hz, $^4J_{HF} = 14.3$ Hz, 2H); ^{13}C NMR ($CDCl_3$) (ppm): δ 150.2 (dd, $^1J_{CF} = 257.6$ Hz, $^2J_{CF} = 43.9$ Hz), 132.7, 129.6, 129.52, 129.48, 128.9, 128.3, 107.4 (m); mp: 115–116 °C; GC–MS, product isomerized on the column, *m*/*z* (relative intensity) of one isomer: 243 ($M^+ + 1$, 18), 242 (M^+, 100), 241 (18), 227 (25), 222 (25), 221 (44), 220 (41), 202 (11), 201 (16), 191 (7), 165 (53), 164 (73), 146 (7), 145 (20), 127 (28), 110(13), 109 (22), 91 (18); the other isomer: 243 ($M^+ + 1$, 24), 242 (M^+, 100), 241 (22), 227 (31), 222 (31), 221 (50), 220 (46), 202 (12), 201 (18), 191 (8), 165 (60), 164

(77), 145 (22), 127 (34), 121 (13), 110 (16), 109 (25), 91 (19); HRMS calculated 242.0907 for $C_{16}H_{12}F_2$, observed 242.0897.

3.2.2. (1Z, 3Z)-1,3-Di(2-chlorophenyl)-2,3-difluoro-butadiene (**3b**)

Similarly, a mixture of 1-bromo-1-fluoro-2-(2-chlorophenyl)ethene (0.47 g, 2.0 mmol, *E*/*Z* = 82:18), bis(tributyltin) (1.14 g, 1.97 mmol), $Pd(PPh_3)_4$ (0.08 g, 0.07 mmol) in DMF (5 ml) was reacted at room temperature for 45 h to give 0.22 g white crystals after a silica gel column (hexanes 100%, $R_f = 0.33$) followed by recrystallization from hexanes. The 71% yield (86% conversion based on the consumed (*E*)-1-bromo-1-fluoroalkene). (1*Z*, 3*Z*) 100%. ^{19}F NMR ($CDCl_3$) (ppm): δ −127.7 (dd, $^3J_{FH(trans)} = 26.5$ Hz, $^4J_{FH} = 14.0$ Hz, 2F); ^{1}H NMR ($CDCl_3$) (ppm): δ 7.90 (dd, $J = 7.7$ Hz, $J = 1.5$ Hz, 2H), 7.42 (dd, $J = 7.8$ Hz, $J = 1.2$ Hz, 2H), 7.29 (t, $J = 7.2$ Hz, 2H), 7.22 (td, $J = 7.8$ Hz, $J = 1.3$ Hz, 2H), 6.73 (dd, $^3J_{HF(trans)} = 27.8$ Hz, $^4J_{FH} = 13.9$ Hz, 2H); ^{13}C NMR ($CDCl_3$) (ppm): δ 150.9 (dd, $^1J_{CF} = 260.0$ Hz, $^2J_{CF} = 43.3$ Hz), 133.8, 130.8 (t, $J = 6.5$ Hz), 130.5, 129.9, 129.4, 127.2, 104.0 (t, $J = 3.0$ Hz); mp: 144–145 °C; GC–MS, *m*/*z* (relative intensity): 314 ($M^+ + 4$, 7), 312 ($M^+ + 2$, 40), 310 (M^+, 61), 277 (22), 275 (63), 155 (14), 240 (66), 239 (77), 238 (100), 221 (18), 220 (88), 219 (17), 218 (14), 199 (13), 198 (10), 164 (34), 163 (14), 119 (94), 109 (26), 97 (20); HRMS calculated 310.0128 for $C_{16}H_{10}{}^{35}Cl_2F_2$, observed 310.0138.

3.2.3. (1Z, 3Z)-2,3-Difluoro-1,3-di(4-methoxyphenyl)-butadiene (**3c**)

Similarly, a mixture of 1-bromo-1-fluoro-2-(4-methoxyphenyl)-ethene (0.46 g, 2.0 mmol, *E*/*Z* = 81:19), bis(tributyltin) (1.13 g, 1.94 mmol), $Pd(PPh_3)_4$ (0.07 g, 0.06 mmol) in DMF (5 ml) was reacted at room temperature for 40 h. ^{19}F NMR showed that the (1*Z*, 3*E*)-diene was also formed in the mixture as a side product; 0.13 g white crystal was obtained after silica gel column chromatography (ethyl acetate:hexanes = 5:95, $R_f = 0.19$) followed by recrystallization from hexanes/ether. The 43% yield (53% conversion based on the consumed (*E*)-1-bromo-1-fluoroalkene). (1*Z*, 3*Z*) 100%. ^{19}F NMR ($CDCl_3$) (ppm): δ −131.2 (dd, $^3J_{FH(trans)} = 29.2$ Hz, $^4J_{FH} = 13.6$ Hz, 2F); ^{1}H NMR ($CDCl_3$) (ppm): δ 7.53 (dm, $J = 8.7$ Hz, 4H), 6.90 (dm, $J = 8.4$ Hz, 4H), 6.13 (dd, $^3J_{HF(trans)} = 29.0$ Hz, $^4J_{HF} = 14.5$ Hz, 2H), 3.83 (d, $J = 0.8$ Hz, 6H); ^{13}C NMR ($CDCl_3$) (ppm): δ 159.5, 149.3 (dd, $^1J_{CF} = 255.0$ Hz, $^2J_{CF} = 45.1$ Hz), 130.8 (t, $J = 2.9$ Hz), 125.7, 114.4, 106.2 (t, $J = 3.8$ Hz); mp: 175–177 °C; GC–MS, *m*/*z* (relative intensity): 303 ($M^+ + 1$, 19), 302 (M^+, 100), 282 (13), 271 (16), 195 (23), 151 (46); HRMS calculated 302.1118 for $C_{18}H_{16}O_2F_2$, observed 302.1118.

3.2.4. (1Z, 3Z)-1,3-Di(4-chlorophenyl)-2,3-difluoro-butadiene (**3d**)

Similarly, a mixture of 1-bromo-1-fluoro-2-(4-chlorophenyl)-ethene (0.188 g, 0.8 mmol, *E*/*Z* = 88:12, the amount of (*E*) isomer is 0.704 mmol), bis(tributyltin) (0.490 g, 0.845 mmol), $Pd(PPh_3)_4$ (0.033 g, 0.028 mmol) in DMF (4 ml) was reacted at room temperature for 41 h. After silica gel column chromatography (hexanes 100%, $R_f = 0.33$) followed by recrystallization from hexanes, 0.09 g white crystals was obtained, yield 72% (82% conversion based on the amount of the consumed (*E*)-1-bromo-1-fluoroalkene). (1*Z*, 3*Z*) 100%. ^{19}F NMR ($CDCl_3$) (ppm): δ −128.1 (dd, $^3J_{FH(trans)} = 28.7$ Hz, $^4J_{FH} = 14.9$ Hz, 2F); ^{1}H NMR ($CDCl_3$) (ppm): δ 7.52 (dm, $J = 8.4$ Hz, 4H), 7.35 (dm, $J = 8.6$ Hz, 4H), 6.20 (dd, $^3J_{HF(trans)} = 28.1$ Hz, $^4J_{HF} = 14.2$ Hz, 2H); ^{13}C NMR ($CDCl_3$) (ppm): δ 132.4 (d, $^1J_{CF} = 237.3$ Hz), 130.55, 130.50, 128.9, 106.5; GC–MS, *m*/*z* (relative intensity): 314 ($M^+ + 4$, 11), 313 (10), 312 ($M^+ + 2$, 64), 311 (15), 310 (M^+, 97), 277 (23), 275 (68), 240 (96), 239 (70), 238 (53), 221 (20), 220 (100), 200 (9), 199 (13), 198 (16), 164 (30), 163 (16), 119 (52), 110 (15), 109 (14); HRMS calculated 310.0128 for $C_{16}H_{10}{}^{35}C1_2F_2$, observed 310.0117.

3.2.5. (1Z, 3Z)-2,3-Difluoro-1,4-di(4-fluorophenyl)-butadiene (**3e**)

Similarly, a mixture of 1-bromo-1-fluoro-2-(4-fluorophenyl)-ethylene (0.175 g, 0.8 mmol, *E*/*Z* = 87:13, the amount of (*E*) isomer is 0.696 mmol), bis(tributyltin) (0.484 g, 0.835 mmol), $Pd(PPh_3)_4$ (0.032 g, 0.028 mmol) in DMF (4 ml) was reacted at room temperature for 53 h. After silica gel column chromatography (hexanes 100%, $R_f = 0.35$) followed by recrystallization from hexanes, 0.08 g white crystals was obtained, yield 72% (83% conversion based on the amount of the consumed (*E*)-1-bromo-1-fluoroalkene). (1*Z*, 3*Z*) 100%. ^{19}F NMR ($CDCl_3$) (ppm): δ −122.8 (m, 2F), −129.8 (dd, $^3J_{FH(trans)} = 28.9$ Hz, $^4J = 14.8$ Hz, 2F); ^{1}H NMR ($CDCl_3$) (ppm): δ 7.57 (ddm, $J = 8.9$ Hz, $J = 5.5$ Hz, 4H), 7.07 (tt, $J = 8.7$ Hz, $J = 5.0$ Hz, 4H), 6.19 (dd, $^3J_{HF(trans)} = 28.3$ Hz, $^4J = 14.2$ Hz, 2H); ^{13}C NMR ($CDCl_3$) (ppm): δ 162.3 (d, $^1J_{CF} = 248.7$ Hz), 149.6 (dd, $^1J_{CF} = 256.2$ Hz, $^2J = 43.6$ Hz), 131.0 (pentet, $J = 4.1$ Hz), 128.6 (d, $J = 2.0$ Hz), 115.8 (d, $J = 20.7$ Hz), 106.1; mp: 154–156 °C; GC–MS, *m*/*z* (relative intensity): 279 ($M^+ + 1$, 22), 278 (M^+, 100), 277 (13), 258 (36), 257 (46), 256 (47), 245 (14), 238 (22), 183 (38), 182 (47), 163 (14), 145 (23), 139 (16), 127 (19), 119 (14), 109 (13); HRMS calculated 278.0719 for $C_{16}H_{10}F_4$, observed 278.0704.

3.2.6. (1Z, 3Z)-2,3-Difluoro-1,4-di(3-nitrophenyl)-butadiene (**3f**)

Similarly, a mixture of 1-bromo-1-fluoro-2-(3-nitrophenyl)-ethene (0.302 g, 1.23 mmol, *E*/*Z* = 81:19, the amount of (*E*) isomer is 1.0 mmol), bis(tributyltin) (0.696 g, 1.20 mmol), $Pd(PPh_3)_4$ (0.046 g, 0.04 mmol) in DMF (5 ml) was reacted at room temperature (use aluminum foil to cover the reaction container) for 130 h. After silica gel column chromatography (ethyl acetate:hexanes = 20:80, $R_f = 0.33$) followed by recrystallization from ether, 0.11 g yellow solid was obtained, yield 54% (66% conversion based on the amount of the consumed (*E*)-1-bromo-1-fluoroalkene). (1*Z*, 3*Z*) 100%. ^{19}F NMR ($CDCl_3$) (ppm): δ −125.8 (dd, $^3J_{FH(trans)} = 27.1$ Hz, $^4J_{FH} = 14.0$ Hz, 2F); ^{1}H NMR ($CDCl_3$) (ppm): δ 8.49 (m, 2H), 8.18 (dd, $J = 7.9$ Hz, $J = 1.9$ Hz, 2H), 7.91 (d, $J = 7.9$ Hz, 2H), 7.59 (t, $J = 8.0$ Hz, 2H), 6.41 ($^3J_{HF(trans)} = 27.1$ Hz, $^4J_{HF} = 14.0$ Hz, 2H); ^{13}C NMR ($CDCl_3$) (ppm): δ 134.9,

133.6, 129.7, 124.0 (m), 123.0, 106.7; mp: 213–215 °C; GC–MS, *m/z* (relative intensity): 333 (M^+ + 1, 3), 332 (M^+, 100), 315 (15), 272 (13), 239 (28), 238 (68), 227 (25), 207 (22), 163 (18), 151 (18), 97 (15), 57 (22). HRMS calculated 332.0609 for $C_{16}H_{10}N_2O_4F_2$, observed 332.0610.

3.2.7. (3Z, 5Z)-4,5-Difluoro-2,7-diphenyl-octa-3,5-diene (**3g**)

Similarly, a mixture of 1-bromo-1-fluoro-3-pheny-1-butene (0.229 g, 1.0 mmol, *E*/*Z* = 83:17, the amount of (*E*) isomer is 0.830 mmol), bis(tributyltin) (0.578 g, 0.996 mmol), $Pd(PPh_3)_4$ (0.038 g, 0.033 mmol) in DMF (3 ml) was reacted at room temperature for 46 h. After silica gel column chromatography (ethyl acetate:hexanes = 3:97, R_f = 0.13), waxy colorless liquid was obtained, 0.10 g, 67% yield (81% conversion based on the consumed (*E*)-1-bromo-1-fluoroalkene). (1*Z*, 3*Z*) 100%. ^{19}F NMR ($CDCl_3$) (ppm): δ −133.0 (dd, $^3J_{FH(trans)}$ = 26.7 Hz, $^4J_{FH}$ = 12.8 Hz); ^{1}H NMR ($CDCl_3$) (ppm): δ 7.16–7.34 (m, 10H), 5.36 (ddd, $^3J_{HF(trans)}$ = 26.5 Hz, $^4J_{HF}$ = 13.3 Hz, $^3J_{HH}$ = 9.9 Hz, 2H), 3.98 (dq, *J* = 9.9 Hz, *J* = 7.1 Hz, 2H), 0.87 (d, *J* = 7.4 Hz, 6H); ^{13}C NMR ($CDCl_3$) (ppm): δ 148.5 (dd, $^1J_{CF}$ = 245.6 Hz, $^2J_{CF}$ = 46.9 Hz), 145.0 (d, *J* = 7.3 Hz), 128.6, 126.8, 126.4, 112.2 (dd, *J* = 6.3 Hz, *J* = 2.5 Hz); GC–MS, *m/z* (relative intensity): 298 (M^+, 5), 283 (5), 263 (3), 220 (20), 193 (22), 165 (31), 149 (18), 134 (15), 133 (23), 129 (28), 115 (22), 105 (100), 103 (22), 91 (64), 77 (32). HRMS calculated 298.1533 for $C_{20}H_{20}F_2$, observed 298.1530.

3.3. General procedures for the preparation of (1E, 3E)-dienes (**6**)

A 25 ml dry round-bottom flask equipped with a stirring bar and a N_2 tee, was charged with $Pd(PPh_3)_4$ (0.046 g, 0.04 mmol) and dry DMF (4 ml). A mixture of (*Z*)-1-bromo-1-fluoroalkene (includes (*Z*)-1-bromo-1-fluoroalkene 1.0 mmol) and the reduced products was added and the solution was stirred at room temperature for 15 min. After the addition of $Bu_3SnSnBu_3$ (0.696 g, 1.2 mmol) and CuI (0.095 g, 0.5 mmol), the reaction mixture was allowed to stir at room temperature. When the reaction was completed, $Co(OAc)_2{\cdot}4H_2O$ (1.25 g, 5.0 mmol) was added to remove the tributyltin halides from the reaction mixture [44]. Silica gel column chromatography followed by recrystallization (if necessary) gave pure products.

3.3.1. (1E, 3E)-2,3-Difluoro-1,4-diphenyl-butadiene (**6a**)

Similarly, a mixture of 1-bromo-1-fluoro-2-phenyl-ethene (include (*Z*)-1-bromo-1-fluoroalkene 0.161 g, 0.8 mmol, *E*/*Z* = 0:100) and the reduced products, bis(tributyltin) (0.557 g, 0.96 mmol), CuI (0.152 g, 0.80 mmol), $Pd(PPh_3)_4$ (0.092 g, 0.08 mmol) in DMF (4 ml) was reacted at room temperature for 39 h. After silica gel column chromatography (ethyl acetate:-hexanes = 3:97, R_f = 0.38), the desired product was obtained as a slight yellow liquid, 0.09 g, 93% yield. ^{19}F NMR ($CDCl_3$) (ppm): δ −109.7 (dd, $^3J_{FH(cis)}$ = 12.1 Hz, $^4J_{FH}$ = 6.6 Hz, 2F); ^{1}H NMR ($CDCl_3$) (ppm): δ 7.17–7.19 (m, 10H), 6.53 (dd, $^3J_{HF(cis)}$ = 10.9 Hz, $^4J_{HF}$ = 6.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) (ppm): δ 148.6 (dd, $^1J_{CF}$ = 251.4 Hz, $^2J_{CF}$ = 39.4 Hz), 130.4 (t, *J* = 3.5 Hz), 127.3, 127.2 (d, *J* = 2.5 Hz), 126.9, 115.4 (dd, $^2J_{CF}$ = 18.1 Hz, $^3J_{CF}$ = 12.9 Hz); GC–MS, *m/z* (relative intensity): 243 (M^+ + 1, 33), 242 (M^+, 89), 241 (40), 227 (52), 222 (46), 221 (63), 220 (71), 202 (19), 201 (35), 165 (48), 164 (100), 145 (36), 127 (39), 109 (31), 91 (25); HRMS calculated 242.0907 for $C_{16}H_{12}F_2$, observed 242.0915.

3.3.2. (1E, 3E)-1,4-Di(2-chlorophenyl)-2,3-difluoro-butadiene (**6b**)

Similarly, a mixture of 1-bromo-1-fluoro-2-(2-chlorophenyl)-ethene (includes (*Z*)-1-bromo-1-fluoroalkene 0.188 g, 0.8 mmol, *E*/*Z* = 0:100), bis(tributyltin) (0.557 g, 0.96 mmol), CuI (0.076 g, 0.40 mmol), $Pd(PPh_3)_4$ (0.037 g, 0.032 mmol) in DMF (4 ml) reacted at room temperature for 44 h. After silica gel column chromatography (hexanes 100%, R_f = 0.39) followed by recrystallization from hexanes, the desired product was obtained as white crystals, 0.11 g, 88% yield. ^{19}F NMR ($CDCl_3$) (ppm): δ −111.2 (dd, $^3J_{FH(cis)}$ = 11.9 Hz, $^4J_{FH}$ = 7.6 Hz, 2F); ^{1}H NMR ($CDCl_3$) (ppm): δ 7.25 (m, 2H), 7.07–7.12 (m, 6H), 6.59 (dd, $^3J_{HF(cis)}$ = 10.8 Hz, $^4J_{HF}$ = 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$) (ppm): δ 150.1 (dd, $^1J_{CF}$ = 253.3 Hz, $^2J_{CF}$ = 36.0 Hz), 133.3 (m), 130.1 (t, *J* = 5.0 Hz), 129.6, 129.2, 128.9, 126.8, 113.6 (dd, *J* = 19.3 Hz, *J* = 14.6 Hz); mp: 84–86 °C; GC–MS, *m/z* (relative intensity): 314 (M^+ + 4, 7), 313 (7), 312 (M^+ + 2, 41), 311 (9), 310 (M^+, 63), 277 (25), 275 (69), 257 (6), 255 (17), 240 (72), 239 (81), 238 (100), 221 (20), 220 (92), 218 (20), 200 (9), 199 (16), 198 (13), 164 (38), 163 (15), 143 (11), 119 (72), 109 (18); HRMS calculated 310.0128 for $C_{16}H_{10}F_2{}^{35}Cl_2$, observed 310.0120.

3.3.3. (1E, 3E)-2,3-Difluoro-1,4-di(4-methoxyphenyl)-butadiene (**6c**)

Similarly, a mixture of 1-bromo-1-fluoro-2-(4-methoxypheny)-ethene (includes (*Z*)-1-bromo-1-fluoroalkene 0.231 g, 1.0 mmol, *E*/*Z* = 0:100), bis(tributyltin) (1.044 g, 1.20 mmol), CuI (0.245 g, 1.25 mmol), $Pd(PPh_3)_4$ (0.115 g, 0.10 mmol) in DMF (4 ml) reacted at room temperature for 20 h. After silica gel column chromatography (ethyl acetate:hexanes = 15:85, R_f = 0.33), the desired product was obtained (contains 6% of impurity which could not be completely separated) as a slightly yellow liquid, 0.08 g, 53% yield. ^{19}F NMR ($CDCl_3$) (ppm): δ −111.2 (dd, *J* = 10.7 Hz, *J* = 5.7 Hz, 2F); ^{1}H NMR ($CDCl_3$) (ppm): δ 7.17(d, *J* = 8.8 Hz, 4H), 6.74 (d, *J* = 8.5 Hz, 4H), 6.49 (dd, *J* = 11.2 Hz, *J* = 6.2 Hz, 2H), 3.75 (d, *J* = 0.7 Hz, 6H); ^{13}C NMR ($CDCl_3$) (ppm): δ 159.3, 148.5 (dd, $^1J_{CF}$ = 249.7 Hz, $^2J_{CF}$ = 39.1 Hz), 129.5 (d, *J* = 1.9 Hz), 123.6 (t, *J* = 4.2 Hz), 115.7 (dd, *J* = 20.3 Hz, *J* = 14.8 Hz), 113.7, 55.0; GC–MS, *m/z* (relative intensity): 303 (M^+ + 1, 18), 302 (M^+, 100), 301 (9), 287 (11), 282 (17), 271 (19), 239 (14), 214 (10), 207 (13), 201 (16), 195 (31), 194 (20), 180 (14), 157 (14), 151 (35); HRMS calculated 302.1118 for $C_{18}H_{16}O_2F_2$, observed 302.1112.

Acknowledgement

We gratefully appreciate the financial support from the National Science Foundation.

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