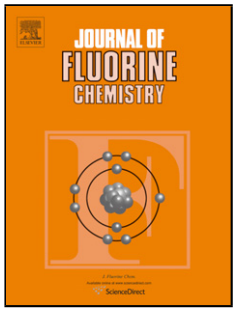

Title: Highly stereoselective approach to 3-fluoroalkylated (*E*)-hex-3-ene-1,5-diyne derivatives *via* an addition-elimination reaction

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Graphical Abstract

Research Highlights

- Fluoroalkylated *cis*-enediynes are prepared *via* the highly stereoselective addition-elimination reaction.
- The stereoselectivity is approximately (*E*)/(*Z*) = >95/5
- Various *cis*-enediynes are prepared only in 5 steps.

Highly stereoselective approach to 3-fluoroalkylated (*E*)-hex-3-ene-1,5-diyne derivatives *via* an addition-elimination reaction

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Abstract: Palladium(0)-catalyzed Sonogashira cross-coupling reaction of 2-fluoroalkylated (*Z*)-2-fluoro-1-iodoethene, which is easily prepared from commercially available polyfluorinated alcohols in facile three steps, with terminal alkynes in DMF at room temperature for 24 h took place stereospecifically to give the corresponding 1-fluoroalkylated (*Z*)-1-fluorobut-1-en-3-yne derivatives in good to excellent yield. Thus obtained fluoroalkylated 1-fluoroenynes were effectively subjected to addition-elimination reaction with various alkynyllithiums at room temperature, leading to 3-fluoroalkylated hex-3-ene-1,5-diyne derivatives in good to high yields with an excellent *E* selectivity.

Keyword : Addition-elimination reaction, Fluorinated alkenes, Fluoroalkylated enediyne compounds, Fluorine-containing enyne compounds, Alkynyllithiums

1. Introduction

cis-Enediyne structures have been frequently found in natural products as antitumor active compounds, such as Esperamicin A_1 and Dynemicin A [1], whose biological activity is derived from the formation of *p*-benzyne (1,4-dehydrobenzene diradical) *via* Bergman cycloaromatization of the enediyne unit [2]. Thus, the generated diradical can abstract hydrogen atoms from the two strands of the DNA duplex, causing double strand DNA cleavage and subsequent apoptosis, that is, self-programmed cell death [3]. In addition, the *cis*-isomers are also recognized in a synthetic organic chemistry as extremely useful precursors for the construction of aromatic ring by an electrocyclization, which are frequently used for the preparation of polyaromatic hydrocarbons (PAHs) [4]. Therefore, it is not surprising that numerous synthetic approaches to non-fluorinated enediyne compounds have been developed so far. Nevertheless, there have been quite a limited number of studies on the synthesis of fluoroalkylated enediyne molecules (Figure 1) [5, 6], though the introduction of fluorine atom(s) into organic molecules very often changes their physical as well as chemical characteristics significantly, resulting in the discovery of new materials with unique physical properties [7].

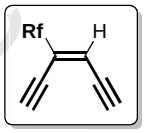
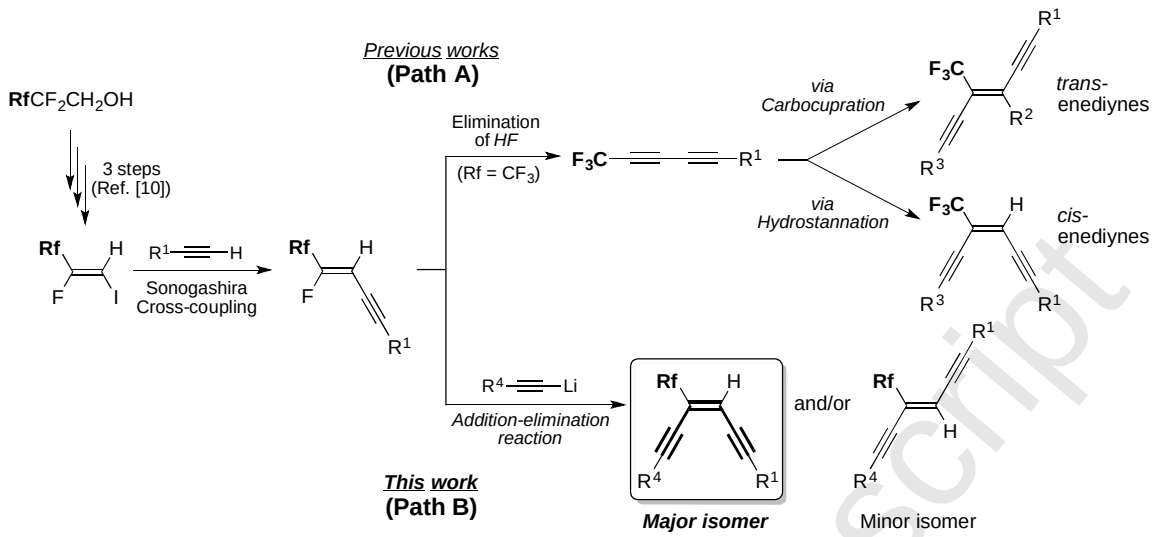


Figure 1. *cis*-3-Fluoroalkyl-hex-3-ene-1,5-diyne compounds

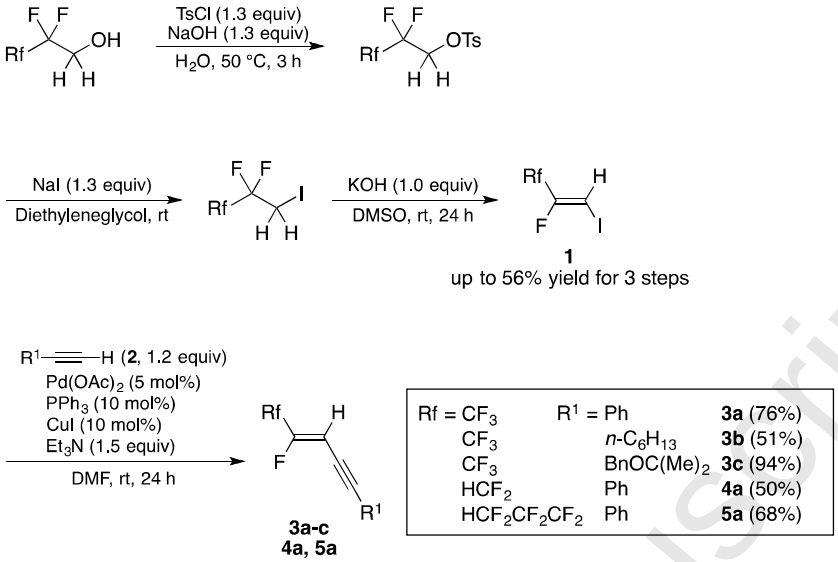
Very recently, we developed efficient synthetic approaches to stereo-defined CF_3-substituted *trans*- and *cis*-enediyne compounds from the CF_3-containing diyne *via* a highly regio- and stereoselective carbocupration and hydrostannation reactions (Scheme 1, Path A) [8]. In the course of our continuous studies on more practical synthesis of such fluoroalkylated enediynes, we wish to report herein an alternative and facile synthetic methods for the preparation of such fluoroalkylated enediyne compounds through a nucleophilic addition-elimination reaction of various alkynyllithiums toward fluorinated alkenes in detail (Scheme 1, Path B) [9].



Scheme 1. Synthetic outline for fluoroalkylated enediyne derivatives

2. Results and discussion

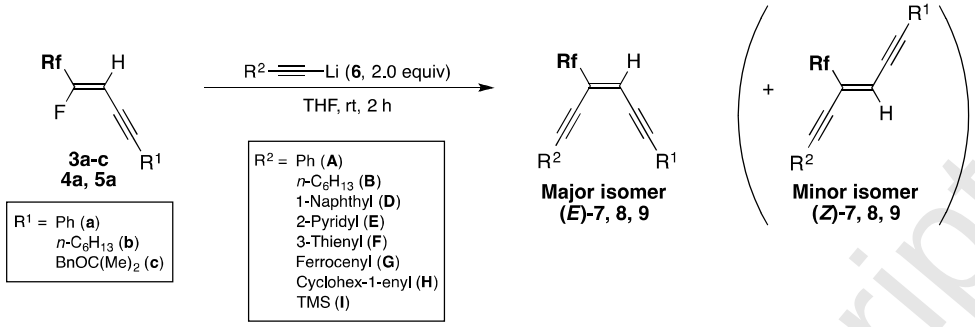
Initially, we started with a preparation of precursors for fluoroalkylated enediyne derivatives, *i.e.* 1-fluoroalkylated (*Z*)-1-fluoro-1-en-3-ynes **3-5,** through Pd(0)-catalyzed Sonogashira cross-coupling reaction of polyfluorinated vinyl iodide **1** with terminal alkynes **2** according to the method developed by our research group [8, 10], and the results are shown in Scheme 2. Thus, commercially available polyfluorinated alcohols [11] were treated with *p*-toluenesulfonyl chloride and NaOH at room temperature to give the corresponding tosylates in quantitative yields, which were subjected to NaI/diethyleneglycol at room temperature, followed by distillation, affording polyfluoroalkyl iodides. Then, the iodides underwent a smooth stereoselective !-elimination reaction by KOH in DMSO, leading to the 2-fluoroalkylated 2-fluoro-1-iodoethenes **1** in good yields. Finally, on treating the iodides **1** with 1.2 equiv of terminal acetylene **2** in the presence of 5 mol% of $Pd(OAc)_2$, 10 mol% each of PPh_3 and CuI, and 1.5 equiv of Et_3N in *N*,*N*-dimethylformamide (DMF) at room temperature for 24 h, the Sonogashira cross-coupling reaction proceeded smoothly to give the corresponding (*Z*)-fluoroalkylated enyne **3a-c**, **4a**, **5a** in good to high isolated yields as a single stereoisomer without any interconversion of *Z* to *E* configuration [12].

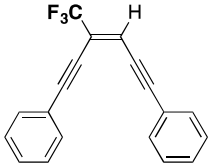


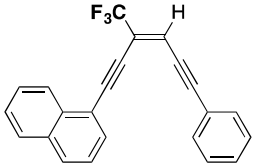
Scheme 2. Preparation of polyfluorinated enynes **3-5**

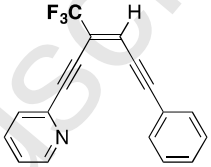
With various substrates in hand, our interest was focused on the synthesis of 3-fluoroalkylated hex-3-ene-1,5-diyne derivatives **7-9** *via* addition-elimination reaction of various alkynyllithiums **6** toward 1-fluoroalkylated (*Z*)-1-fluoro-1-en-3-ynes **3-5**. Thus, the reaction of fluoroalkylated enynes **3-5** with 2.0 equiv of lithium acetylides **6**, readily prepared from terminal alkynes **6** and *n*-butyllithium, was conducted in THF at room temperature for 2 h. The results are listed in Table 1.

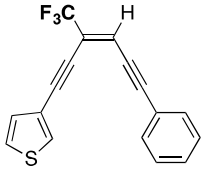
Table 1. Addition-elimination reaction of fluoroalkylated enynes **3-5** with various alkynyllithiums **6**

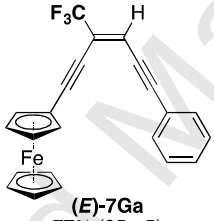


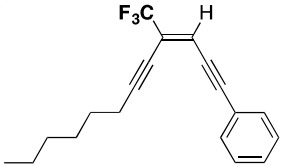

(*E*)-7Aa
73% (98 : 2)

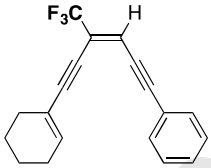

(*E*)-7Da
56% (97 : 3)

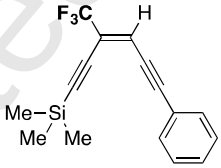

(*E*)-7Ea
35% (83 : 17)

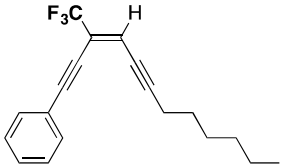

(*E*)-7Fa
69% (95 : 5)

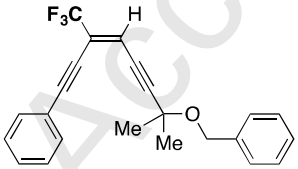

(*E*)-7Ga
77% (95 : 5)

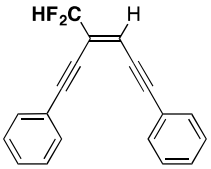

(*E*)-7Ba
56% (96 : 4)

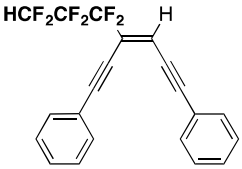

(*E*)-7Ha
82% (96 : 4)


(*E*)-7Ia
21% (93 : 7)


(*E*)-7Ab
65% (96 : 4)


(*E*)-7Ac
68% (97 : 3)


(*E*)-8Aa
74% (92 : 8)

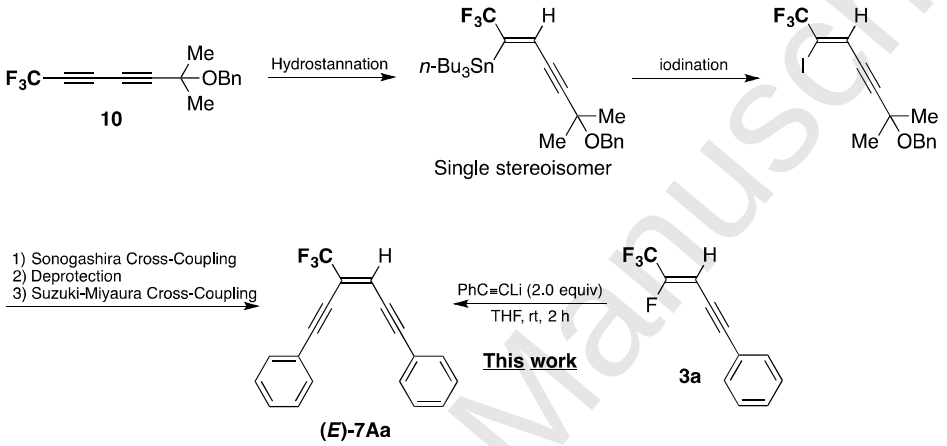

(*E*)-9Aa
44% (94 : 8)

Isolated yields are shown. Values in parentheses are the ratios of (*E*)- and (*Z*)-isomers.

The addition-elimination reaction of trifluoromethylated enyne **3a** with 2.0 equiv of (phenylethynyl)lithium (**6A**) in THF at room temperature for 2 h took place very smoothly to form the corresponding enediyne derivative **7Aa** in 73% isolated yield. We were very delighted to find an excellent *E* selective formation of **7Aa** (*E:Z* = 98:2). Various alkynyllithiums having an aromatic ring on the terminus, such as 1-naphthyl (**6D**), 3-thienyl (**6F**), ferrocenyl (**6G**), as R^2 could effectively take part in the addition-elimination reaction, the corresponding products **7Da**, **7Fa**, and **7Ga** being obtained in 56-77% yields in a highly *E* selective fashion. The alkyl or alkenyl substituents like *n*-hexyl (**6B**) or cyclohex-1-enyl (**6H**) on alkynyllithium did not cause any significant influence on the addition-elimination reaction though the substituent such as 2-pyridyl (**6E**) and trimethylsilyl (**6I**) resulted in a significant decrease of the yield and stereoselectivity. Trifluoromethylated enynes **3b** or **3c** carrying a *n*-hexyl or a (benzyloxy)dimethylmethyl group on the alkyne terminus also underwent the smooth addition-elimination reaction with acetylide **6A**, giving rise to the corresponding **7Ab** and **7Ac** in good yields with an excellent *E* selectivity (*E:Z* = >96:4). Other fluoroalkylated enyne compounds, such as difluoromethylated and hexafluoropropylated enynes, **4a** and **5a**, was also subjected to the stereoselective addition-elimination reaction, yielding the corresponding addition-elimination products **8Aa** and **9Aa** in 74% (*E/Z* = 92/8) and 44% (*E/Z* = 94/6) yields, respectively.

The stereochemistry of the obtained enediynes was made as follows (Scheme 3 and Figure 2). Thus, the major product of **7Aa** is a known compound, which can be prepared from CF_3-containing diyne **10** *via* a highly regio- and stereoselective hydrostannation reaction in six steps, as shown in Scheme 3 [8]. Thus, on treating **10** with 1.2 equiv of *n*-Bu_3SnH in the presence of 20 mol% of Et_3B in toluene at ! 78 °C for 1 h, fortunately, the hydrostannation reaction proceeded quite smoothly to afford the corresponding *trans*-vinylstannane in 75% isolated yield as a sole product. Then, the stereoselectively obtained CF_3-substituted vinylstannane **10** was converted to the corresponding vinyl iodide by treating **10** with iodine in CH_2Cl_2 at room temperature, which underwent quite smoothly Sonogashira cross-coupling reaction with phenylacetylene, giving rise to the corresponding stereo-defined CF_3-substituted *cis*-enediyne compound in 74% isolated yields. Finally, the terminal functional group, *i.e.* $BnOC(Me)_2$, in enediyne was easily convertible to the corresponding **(*E*)-7Aa** enediyne through the deprotection and the subsequent Sonogashira cross-coupling reaction. The comparison of the NMR spectra of the major product in **7Aa** starting from **3a** with the one starting from **10** made it possible to determine the double bond configuration of the

major product in **7Aa** as *E*. Additionally, it was observed in ^{1}H NMR spectra that the signal of H_a could be barely observed as quartet/multiplet (Rf = CF_3 and $HCF_2CF_2CF_2$), or triplet (Rf = HCF_2) in almost all of the major isomers, as shown in Figure 2. This fact strongly indicates that the spin-spin splitting of H_a signal might be derived from the interaction between H_a and a fluoroalkyl group, suggesting that the addition-elimination products have an *E* configuration.



Scheme 3. Determination of the stereochemistry

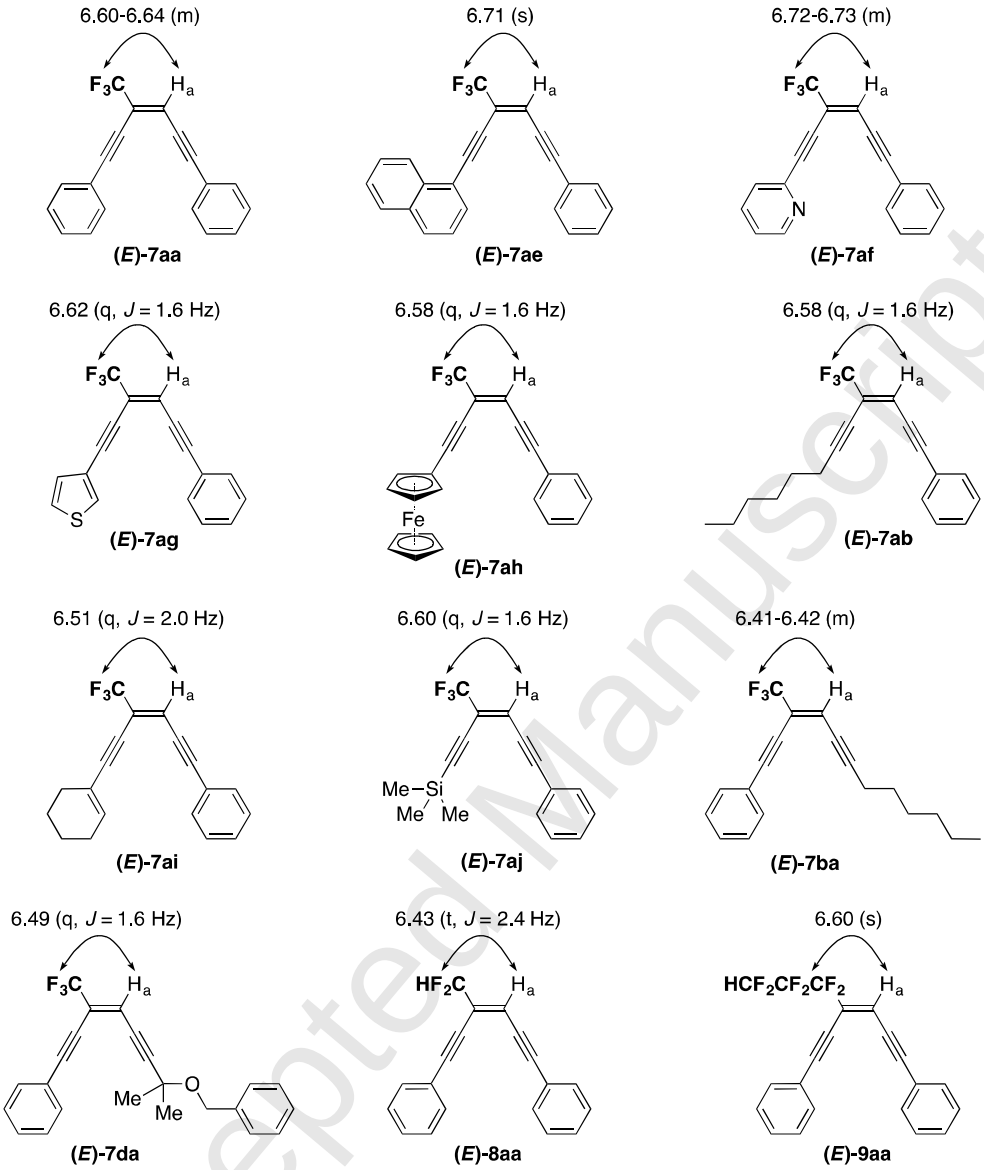
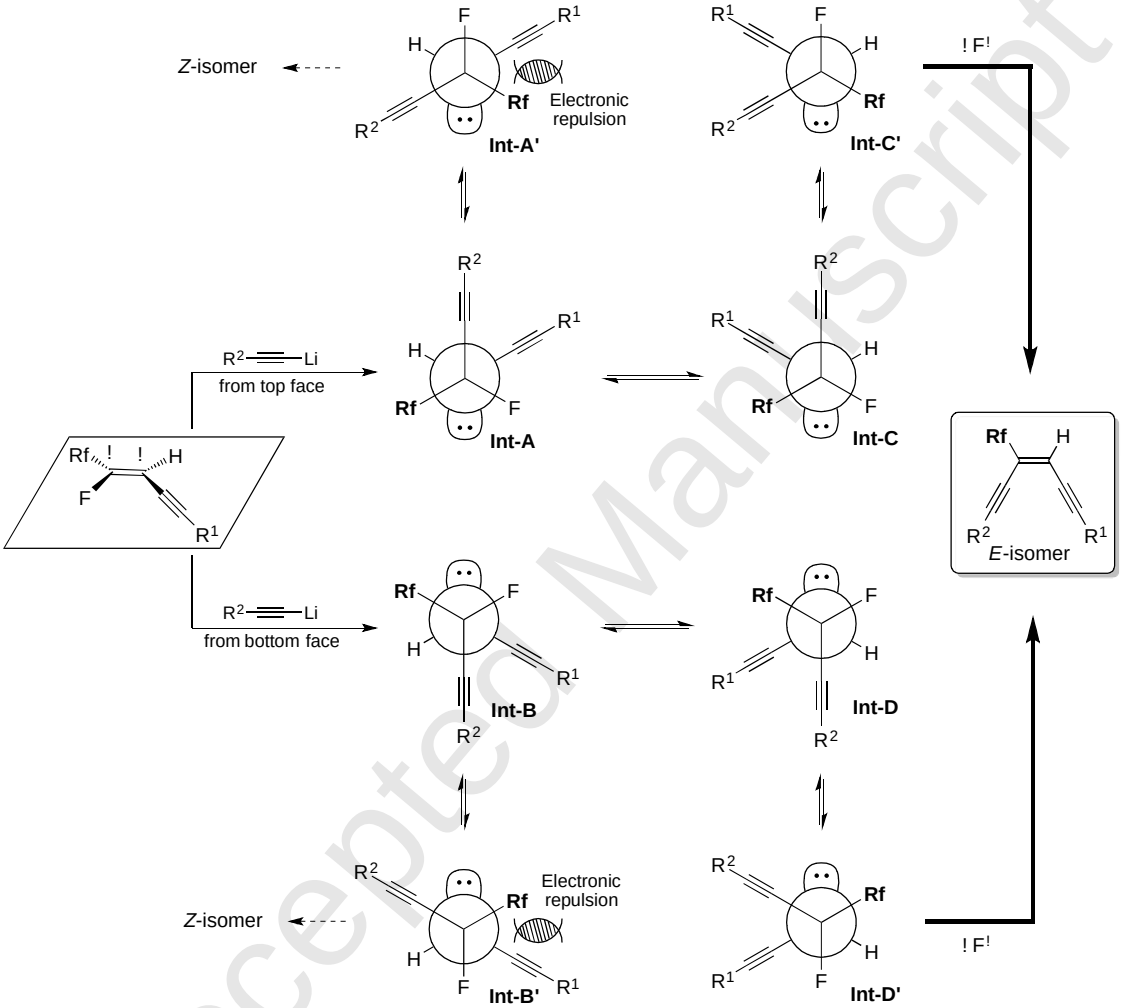


Figure 2. Interaction between H_a and a fluoroalkyl group

The excellent *E* selectivity on the addition-elimination reaction could be rationalized by the formation of stable carbanion intermediates, followed by the *anti*-elimination of LiF. The possible reaction mechanism is illustrated in Scheme 4 [6a].



Scheme 4. A possible reaction mechanism for *E*-selective addition-elimination reaction (Li cation was omitted for clarification.)

A nucleophilic attack of alkynyllithium to an ! -carbon on the enyne substrate could form conformational intermediates **Int-A** (attacked from top face) or **Int-B** (attacked from bottom face), which is in equilibrium with either **Int-C** or **Int-D** due to a resonance effect. Their intermediates **Int-A** to **Int-D** would rotate 60° so that an elimination of LiF proceeds *via anti*-elimination, giving rise to an intermediate **Int-A'** to **Int-D'**. Among them, **Int-C'** and **Int-D'** would be much more favorable than the others because there is no electronic gauche repulsion between an alkynyl and an

electronic bulkyl fluoroalkyl groups. As a consequence, an immediate *anti*-elimination of LiF from preferentially formed **Int-C'** and **Int-D'** proceeds to give enediyne compounds with an excellent *E* selectivity.

3. Conclusion

In conclusion, we have described an effective preparation of (*Z*)-1-fluoroalkylated 1-fluoroenyne compounds by Pd(0)-catalyzed cross-coupling reaction of 2-fluoroalkylated 2-fluoro-1-iodoethene with terminal alkynes. Thus obtained 1-fluoroalkylated 1-fluoroenynes were subjected to the addition-elimination reaction with various types of alkynyllithiums, leading to the corresponding 3-fluoroalkylated hex-3-ene-1,5-diyne derivatives in good yields with an excellent *E* selectivity. We believe that the present *E*-selective synthetic procedure for fluoroalkylated enediyne delivatives would facilitate to open avenues to fluorine-containing biologically active compounds.

4. Experimental

4.1. General procedures

Infrared spectra (IR) were determined in a liquid film on a NaCl plate or KBr disk method with a JASCO FT/IR-4100 typeA spectrometer. ^{1}H and ^{13}C NMR spectra were measured with a JEOL JNM-AL400 NMR spectrometer in a chloroform-*d* ($CDCl_3$) solution with tetramethylsilane (Me_4Si) as an internal reference. A JEOL JNM-EX90A (84.21 MHz) FT-NMR spectrometer and a JEOL JNM-AL400 NMR spectrometer were used for determining the yields of the products with hexafluorobenzene (C_6F_6). ^{19}F NMR (376.05 MHz) spectra were measured with a JEOL JNM-AL 400 NMR spectrometer in a chloroform-*d* ($CDCl_3$) solution with trichlorofluoromethane ($CFCl_3$) as an internal standard. High-resolution mass spectra (HRMS) were taken on a JEOL JMS-700MS spectrometer by electron impact (EI), chemical ionization (CI), and fast atom bombardment (FAB) methods.

All reactions were routinely monitored by ^{19}F NMR spectroscopy or TLC, and carried out under an atmosphere of argon.

4.1.1. Materials

N,N-Dimethylformamide (DMF), triethylamine (Et_3N), and hexamethylphosphoric triamide (HMDS) were fleshly distilled from calcium hydride (CaH_2). All chemicals were of reagent grade and, if necessary, were purified in the usual manner prior to use. Thin-layer chromatography (TLC) was done with Merck silica gel 60 F_{254} plates, and column chromatography was carried out using Wako gel C-200 as adsorbent.

4.2. General procedure for the preparation of 2-fluoroalkylated 1-iodo-2-fluoroethene ***1***

The starting polyfluorinated vinyl iodides 1 were prepared from easily available polyfluorinated alcohols with 3 steps according to the reported procedure, as follows: Polyfluorinated alcohol (1.0 mol) and *p*-toluenesulfonyl chloride (1.2 mol) was dissolved in H_2O (350 mL), and dropwise the whole was heated at 50 °C. To the solution was added slowly a NaOH solution (150 mL, 1.2 mol). After stirring of the reaction mixture for 3 h, the reaction mixture was cooled to room temperature, followed by extraction with Et_2O three times. The combined organic layers were washed with NH_3 aq. (twice), ten H_2O (three times), and dried over anhydrous Na_2SO_4. After evaporation of the organic materials, the residue and NaI (180 g, 1.2 mol) was dissolved in diethyleneglycol (350 mL). The solution was heated (bath temperature *ca*. 170 °C/760 mmHg) to distill the desired iodide, which was washed with water six times. The crude materials were dissolved in DMSO (250 mL), and to this reaction mixture was added a KOH solution (100 mL, 0.9 mol) at 0-10 °C. After stirring of the reaction mixture for 24 h, the reaction mixture was heated at 80-100 °C to obtain the light-red oil, which was washed with H_2O, dried over anhydrous Na_2SO_4, then filtered to afford the desired polyfluorinated vinyl iodide **1**. The characterization data for **1** were in accordance with a previously reported data, see: Ref. [10].

*4.3. Typical procedure for the preparation of (Z)-1,1,1,2-tetrafluoro-5-phenyl-2-penten-4-yne (**3a**)*

In a two-necked round-bottomed flask equipped with a magnetic stirrer bar, a rubber septum, and an inlet tube for Ar, was charged with a solution of $Pd(OAc)_2$ (224 mg, 1.0 mmol) and PPh_3 (525 mg, 2.0 mmol) in DMF (133 mL). To a solution of prepared Pd(0) catalyst in advance was added 1-iodo-2,3,3,3-tetrafluoroprop-1-ene (4.80 g, 20 mmol), followed by continuous stirring for 20 min at room temperature. After that, ethynylbenzene (2.6 mL, 2.45 g, 24 mmol), Et_3N (4.2 mL, 3.07 g, 30 mmol), and CuI (381 mg, 2 mmol) was added in this order into the above mixture. The whole was

stirred for 24 h before quenching with saturated aqueous NH_4Cl solution. The mixture was extracted with Et_2O three times, and the combined organic layers were dried over anhydrous Na_2SO_4, then filtered. The filtrate was evaporated to give the corresponding crude materials, which was purified by silica gel column chromatography, affording the 1,1,1,2-tetrafluoro-5-phenyl-2-penten-4-yne (**3a**, 2.71 g, 12.65 mmol, 76% yield).

*4.3.1. (Z)-1,1,1,2-Tetrafluoro-5-phenylpent-2-en-4-yne (**3a**)*

^{1}H NMR ($CDCl_3$) ! 5.93 (d, J = 28.8 Hz, 1H), 7.36 – 7.40 (m, 3H), 7.49 – 7.51 (m, 2H); ^{13}C NMR ($CDCl_3$) ! 77.5, 95.1 (dq, J = 3.9, 4.1 Hz), 100.1 (dq, J = 6.5, 1.7 Hz), 118.4 (qd, J = 271.1, 39.8 Hz), 121.8, 128.5, 129.5, 131.9, 152.1 (dq, J = 273.1, 39.3 Hz); ^{19}F NMR ($CDCl_3$) ! ! 120.82 (dq, J = 28.8, 9.8 Hz, 1F), ! 72.99 (d, J = 9.8 Hz, 3F); IR (neat) ! 3074, 2927, 2213, 1685, 1367, 1200, 1149, 1030, 1009, 756 cm^{-1}; HRMS calcd for $C_{11}H_6F_4$ (M+) 214.0406, found 214.0396.

*4.3.2. (Z)-1,1,1,2-Tetrafluoroundec-2-en-4-yne (**3b**)*

^{1}H NMR ($CDCl_3$) ! 0.90 (t, J = 6.80 Hz, 3H), 1.24 – 1.44 (m, 6H), 1.52 – 1.60 (m, 2H), 2.38 (t, J = 7.2 Hz, 2H), 5.68 (d, J = 29.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) ! 14.0, 19.7, 22.5, 28.2, 28.5, 31.3, 69.1, 95.5 (dq, J = 13.7, 3.6 Hz), 102.6 (dq, J = 6.6, 1.6 Hz), 118.5 (qd, J = 271.1, 39.7 Hz), 151.9 (dq, J = 270.4, 38.9 Hz); ^{19}F NMR ($CDCl_3$) ! ! 123.76 (dq, J = 29.2, 9.8 Hz, 1F), ! 73.08 (d, J = 9.8 Hz, 3F) ; IR (neat) ! 3078, 2935, 2862, 2339, 2224, 1685, 1469, 1431, 1372, 1155, 959 cm^{-1}; HRMS calcd for $C_{11}H_{14}F_4Na$ (M+Na) 245.0929, found 245.0940.

*4.3.3. (Z)-6-Benzyloxy-1,1,1,2-tetrafluoro-6-methylhept-2-en-4-yne (**3c**)*

^{1}H NMR ($CDCl_3$) ! 1.59 (s, 6H), 4.63 (s, 2H), 5.76 (d, J = 28.8 Hz, 1H), 7.27 – 7.36 (m, 5H); ^{13}C NMR ($CDCl_3$) ! 28.5, 66.8, 71.0, 81.7, 94.5 – 94.6 (m), 103.0 (d, J = 5.7 Hz), 118.2 (qd, J = 271.2, 39.7 Hz), 127.4, 127.7, 128.3, 138.5, 152.5 (dq, J = 272.6, 39.3 Hz); ^{19}F NMR ($CDCl_3$) ! ! 120.71 (dq, J = 28.8, 9.8 Hz, 1F), ! 73.19 (d, J = 9.8 Hz, 3F); IR (neat) ! 3069, 2988, 2868, 2229, 1684, 1455, 1301, 1111, 929, 846, 697, 661 cm^{-1}; HRMS calcd for $C_{15}H_{14}F_4O$ (M+) 286.0981, found 286.0977.

*4.3.4. (Z)-1,1,2-Trifluoro-5-phenylpent-2-en-4-yne (**4a**)*

^{1}H NMR ($CDCl_3$) ! 5.70 (d, J = 30.4 Hz, 1H), 6.14 (td, J = 53.4, 4.9 Hz, 1H), 7.32 – 7.37 (m, 3H), 7.37 – 7.51 (m, 2H); ^{13}C NMR ($CDCl_3$) ! 78.4 – 78.5 (m, 1C), 93.8 (dt, J = 9.0, 6.6 Hz), 98.3-98.5

(m, 1C), 108.7 (td, *J* = 230.8, 37.2 Hz), 122.1, 128.4, 129.2, 131.8, 157.0 (dt, *J* = 272.7, 25.2 Hz); ^{19}F NMR ($CDCl_3$) ! –124.04 (dd, *J* =53.4, 19.1 Hz, 2F), –117.85 to –117.65 (m, 1F); IR (neat) ! 3061, 2975, 2867, 2373, 2213, 1955, 1683, 1598, 1491, 1402, 1274, 1109, 895 cm^{-1}; HRMS calcd for $C_{11}H_7F_3$ (M+) 196.0500, found 196.0508.

*4.3.5. (Z)-1,1,2,2,3,3,4-Heptafluoro-7-phenylhept-4-en-6-yne (**5a**)*

^{1}H NMR ($CDCl_3$) ! 5.94 (d, *J* = 29.2 Hz, 1H), 6.05 (tt, *J* = 52.0, 5.2 Hz, 1H), 7.34 – 7.39 (m, 3H), 7.49 – 7.55 (m, 2H); ^{13}C NMR ($CDCl_3$) δ = 77.8, 97.3 (dt, *J* = 8.2, 6.2 Hz), 100.4 (m, 1C), 104 – 115 (m, 3C), 121.8, 128.5, 129.5, 131.8, 152.8 (dt, *J* = 272.8, 28.7 Hz); ^{19}F NMR ($CDCl_3$) ! –137.5 to –137.2 (m, 2F), –130.7 to –130.6 (m, 2F), ! 119.8 to ! 119.6 (m, 2F), ! 116.18 to ! 116.00 (m, 1F); IR (neat) ! 3069, 2212, 1674, 1348, 1222, 1163, 1126, 949, 827, 756 cm^{-1}; HRMS calcd for $C_{13}H_8F_7$ (M+H) 297.0514, found 297.0527.

*4.4. Typical procedure for the synthesis of 1,6-diphenyl-3-(trifluoromethyl)hex-3-en-1,5-diyne (**7Aa**)*

In a two-necked round-bottomed flask equipped with a magnetic stirrer bar, a rubber septum, and an inlet tube for Ar, was charged with a solution of ethynylbenzene (82 mg, 0.80 mmol) in THF (2.0 mL). To the solution was added *n*-BuLi (0.5 mL, 0.80 mmol) at 0 °C, followed by stirring at that temperature for 30 min. To the resultant solution was added the 1,1,1,2-tetrafluoro-5-phenylpent-2-en-4-yne (82 mg, 0.37 mmol) at 0 °C. The whole was allowed to warm to room temperature, then being stirred for another 2 h. The reaction was quenched with saturated aqueous NH_4Cl solution and the resultant was extracted with Et_2O three times. The combined organic layers were dried over anhydrous Na_2SO_4, followed by filtered. The filtrate was evaporated to give the crude materials, which was purified by silica gel column chromatography, affording the 1,6-diphenyl-3-(trifluoromethyl)hex-3-en-1,5-diyne (**7Aa**, 83 mg, 0.28 mmol, 73% yield, Isomer ratio, *E*/*Z* =98/2).

*4.4.1. (E)-1,6-Diphenyl-3-(trifluoromethyl)hex-3-en-1,5-diyne (**7Aa**)*

Yield: 73% (*E*:*Z* = 98:2); ^{1}H NMR ($CDCl_3$) ! = 6.60 – 6.64 (m, 1H), 7.35 – 7.42 (m, 6H), 7.52 – 7.57 (m, 4H); ^{13}C NMR ($CDCl_3$) ! = 81.7 (q, *J* = 2.2 Hz), 85.2, 100.2, 102.8, 120.4 (q, *J* = 5.50 Hz), 121.9, 122.9 (q, *J* = 34.7 Hz), 121.6 (q, *J* = 273.1 Hz), 122.1, 128.5, 128.6, 129.5, 129.6, 131.9, 132.0; ^{19}F NMR ($CDCl_3$) ! = –66.55 (s, 3F); IR (neat) ! 3054, 2926, 2244, 2209, 2189, 1952, 1729, 1490, 1391, 916, 864, 754, 687 cm^{-1}; HRMS calcd for $C_{19}H_{11}F_3$ (M+) 296.0813, found 296.0807.

*4.4.2. (E)-1-(1-Naphthyl)-6-phenyl-3-(trifluoromethyl)hex-3-en-1,5-diyne (**7Da**)*

Yield: 56% (*E:Z* = 97:3); ^{1}H NMR ($CDCl_3$) ! 6.71 (s, 1H), 7.34 – 7.57 (m, 8H), 7.80 – 7.92 (m, 3H), 8.40 – 8.45 (m, 1H); ^{13}C NMR ($CDCl_3$) ! 85.5, 86.5 (q, *J* = 2.1 Hz), 98.6, 102.90, 102.92, 119.4, 120.2 (q, *J* = 5.5 Hz), 121.7 (q, *J* = 273.2 Hz), 122.0, 123.1 (q, *J* = 34.4 Hz), 125.2, 126.0, 126.7, 128.3, 128.5, 129.6, 127.4, 130.1, 130.3, 132.3, 133.1; ^{19}F NMR ($CDCl_3$) ! ! 66.34 (s, 3F, *E*-isomer), ! 62.71 (s, 3F, *Z*-isomer); IR (neat) ! 3057, 2206, 2184, 1587, 1410, 1375, 1307, 1135, 1106, 1023, 863 cm^{-1}; HRMS calcd for $C_{23}H_{13}F_3$ (M+) 346.0969, found 346.0977.

*4.4.3. (E)-6-Phenyl-1-(2-pyridyl)-3-(trifluoromethyl)hex-3-en-1,5-diyne (**7Ea**)*

Yield: 35% (*E:Z* = 83:17); ^{1}H NMR ($CDCl_3$) ! 6.72 – 6.73 (m, 1H), 7.29 – 7.40 (m, 4H), 7.55 – 7.60 (m, 3H), 7.66 – 7.74 (m, 1H), 8.66 – 8.72 (m, 1H); ^{13}C NMR ($CDCl_3$) ! 80.7 (q, *J* = 3.0 Hz), 85.0, 98.5, 104.0, 120.1, 121.5 (q, *J* = 273.0 Hz), 122.5 (q, *J* = 34.2 Hz), 122.6 (q, *J* = 5.5 Hz), 123.7, 127.7, 128.5, 129.8, 132.2, 136.1, 142.3, 150.4; ^{19}F NMR ($CDCl_3$) ! ! 66.22 (s, 3F, *E*-isomer), ! 62.74 (s, 3F, *Z*-isomer); IR (neat) ! 3054, 2926, 2191, 1733, 1581, 1464, 1181, 1136, 987, 919, 870 cm^{-1}; HRMS calcd for $C_{18}H_{11}F_3N$ (M+H) 298.0844, found 298.0848.

*4.4.4. (E)-6-Phenyl-1-(3-thienyl)-3-(trifluoromethyl)hex-3-en-1,5-diyne (**7Fa**)*

Yield: 69% (*E:Z* = 95:5); ^{1}H NMR ($CDCl_3$) ! 6.62 (q, *J* = 1.6 Hz, 1H), 7.20 – 7.22 (m, 1H), 7.32 – 7.39 (m, 4H), 7.51 – 7.53 (m, 2H), 7.62 – 7.63 (m, 1H); ^{13}C NMR ($CDCl_3$) ! 81.4 (q, *J* = 2.2 Hz), 85.2, 95.3, 102.7, 120.2 (q, *J* = 5.6 Hz), 121.0, 122.1, 123.9 (q, *J* = 34.7 Hz), 124.4 (q, *J* = 284.5 Hz), 125.8, 128.6, 129.6, 129.7, 130.5, 132.0; ^{19}F NMR ($CDCl_3$) ! ! 66.51 (s, 3F, *E*-isomer), ! 62.91 (s, 3F, *Z*-isomer); IR (neat) ! 3110, 3052, 2213, 2191, 1726, 1603, 1426, 1307, 1136, 1066, 931, 871 cm^{-1}; HRMS calcd for $C_{17}H_9F_3S$ (M+) 302.0377, found 302.0376.

*4.4.5. (E)-1-Ferrocenyl-6-phenyl-3-(trifluoromethyl)hex-3-en-1,5-diyne (**7Ga**)*

Yield: 77% (*E:Z* = 95:5); ^{1}H NMR ($CDCl_3$) ! 4.24 – 4.36 (m, 7H), 4.50 – 4.57 (m, 2H), 6.58 (q, *J* = 1.6 Hz, 1H), 7.35 – 7.40 (m, 3H), 7.53 – 7.58 (m, 2H); ^{13}C NMR ($CDCl_3$) ! 66.9, 69.2, 69.7, 70.1, 70.2, 70.3, 71.9, 72.1, 78.17, 78.19, 85.6, 87.0, 100.7, 104.6, 118.7 (q, *J* = 5.3 Hz), 121.5 (q, *J* = 270.5 Hz), 122.3, 123.5 (q, *J* = 33.6 Hz), 128.5, 129.4, 131.9; ^{19}F NMR ($CDCl_3$) ! ! 66.60 (s, 3F, *E*-isomer), ! 62.93 (s, 3F, *Z*-isomer); IR (neat) ! 3097, 2210, 2192, 1602, 1306, 1135, 1081, 918, 822 cm^{-1}; HRMS calcd for $C_{23}H_{15}F_3Fe$ (M+) 404.0475, found 404.0472.

*4.4.6. (E)-1-Phenyl-4-(trifluoromethyl)dodec-3-en-1,5-diyne (**7Ba**)*

Yield: 56% (*E:Z* = 96:4); ^{1}H NMR ($CDCl_3$) ! 0.86 (t, *J* = 6.99 Hz, 3H), 1.25 – 1.30 (m, 4H), 1.42 – 1.50 (m, 2H), 1.59 – 1.66 (m, 2H), 2.49 (t, *J* = 6.39 Hz, 2H), 6.52 (m, 1H), 7.35 – 7.39 (m, 3H), 7.48 – 7.50 (m, 2H); ^{13}C NMR ($CDCl_3$) ! 14.0, 19.8, 22.5, 28.3, 28.5, 31.3, 73.2 (q, *J* = 2.0 Hz), 85.0, 101.2, 102.7, 119.3 (q, *J* = 5.8 Hz), 121.6 (q, *J* = 268.7 Hz), 123.0, 123.3 (q, *J* = 34.3 Hz), 128.4, 129.4, 132.0; ^{19}F NMR ($CDCl_3$) ! ! 67.13 (s, 3F, *E*-isomer), ! 63.36 (s, 3F, *Z*-isomer); IR (neat) ! 3055, 2932, 2860, 2197, 1604, 1382, 1305, 1136, 1034, 864 cm^{-1}; HRMS calcd for $C_{19}H_{19}F_3$ (M+H) 304.1439, found 304.1431.

*4.4.7. (E)-1-(Cyclohex-1-enyl)-6-phenyl-3-(trifluoromethyl)hex-3-en-1,5-diyne (**7Ha**)*

Yield: 82% (*E:Z* = 96:4); ^{1}H NMR ($CDCl_3$) ! 1.60 – 1.71 (m, 4H), 2.10 – 2.30 (m, 4H), 6.32 – 6.37 (m, 1H), 6.51 (q, *J* = 2.0 Hz, 1H), 7.36 – 7.38 (m, 3H), 7.49 – 7.51 (m, 2H); ^{13}C NMR ($CDCl_3$) ! 21.3, 22.1, 25.9, 28.7, 79.4 (q, *J* = 2.5 Hz), 85.3, 102.0, 102.5, 119.0 (q, *J* = 5.8 Hz), 120.2, 121.6 (q, *J* = 272.8 Hz), 123.3 (q, *J* = 34.7 Hz), 128.5, 129.4, 132.0, 138.3; ^{19}F NMR ($CDCl_3$) ! ! 66.78 (s, 3F, *E*-isomer), ! 63.12 (s, 3F, *Z*-isomer); IR (neat) ! 2933, 2861, 2181, 1577, 1394, 1307, 1138, 1061, 788 cm^{-1}; HRMS calcd for $C_{19}H_{15}F_3$ (M+) 300.1126, found 300.1130.

*4.4.8. (E)-6-Phenyl-3-(trifluoromethyl)-1-(trimethysilyl)hex-3-en-1,5-diyne (**7Ia**)*

Yield: 21% (*E:Z* = 93:7); ^{1}H NMR ($CDCl_3$) ! 0.27 (s, 9H), 6.60 (q, *J* = 1.6 Hz), 7.35 – 7.40 (m, 3H), 7.49 – 7.51 (m, 2H); ^{13}C NMR ($CDCl_3$) ! -0.38, 85.0, 95.9 (q, *J* = 2.2 Hz), 102.8, 107.3, 121.5 (q, *J* = 273.1 Hz), 121.7 (q, *J* = 5.8 Hz), 122.1, 122.9 (q, *J* = 33.9 Hz), 128.5, 129.6, 132.1; ^{19}F NMR ($CDCl_3$) ! ! 66.64 (s, 3F, *E*-isomer), ! 63.04 (s, 3F, *Z*-isomer); IR (neat) ! 2963, 2201, 1603, 1584, 1367, 1306, 1139, 1006, 868 cm^{-1}; HRMS calcd for $C_{16}H_{15}F_3Si$ (M+) 292.0895, found 292.0905.

*4.4.9. (E)-1-Phenyl-3-(trifluoromethyl)dodec-3-en-1,5-diyne (**7Ab**)*

Yield: 65% (*E:Z* = 96:4); ^{1}H NMR ($CDCl_3$) ! 0.86 (t, *J* = 6.99 Hz, 3H), 1.24 – 1.62 (m, 8H), 2.46 – 2.50 (m, 2H), 6.41 – 6.42 (m, 1H), 7.33 – 7.38 (m, 3H), 7.50 – 7.53 (m, 2H); ^{13}C NMR ($CDCl_3$) ! 14.0, 20.1, 22.5, 28.4, 28.5, 31.3, 81.4, 81.5, 98.8, 105.8 (q, *J* = 1.6 Hz), 121.5 (q, *J* = 5.5 Hz), 122.01 (q, *J* = 272.8 Hz), 122.02, 122.3 (q, *J* = 33.3 Hz), 128.4, 129.3, 131.9; ^{19}F NMR ($CDCl_3$) ! ! 66.63 (s, 3F, *E*-isomer), ! 63.05 (s, 3F, *Z*-isomer); IR (neat) ! 2932, 2860, 2219, 1589, 1396, 1289, 1138, 1039, 869 cm^{-1}; HRMS calcd for $C_{19}H_{19}F_3O$ (M+) 304.1439, found 304.1443.

*4.4.10. (E)-7-Benzyloxy-7-methyl-1-phenyl-3-(trifluoromethyl)oct-3-en-1,5-diyne (**7Ac**)*

Yield: 68% (*E:Z* = 97:3); ^{1}H NMR ($CDCl_3$) ! = 1.65 (s, 6H), 4.69 (s, 2H), 6,49 (q, *J* = 1.60 Hz, 1H), 7.26 – 7.47 (m, 10H); ^{13}C NMR ($CDCl_3$) ! = 28.7, 66.9, 71.2, 80.1, 81.2 (q, *J* = 2.2 Hz), 99.8, 105.3, 120.0 (q, *J* = 5.5 Hz), 121.5 (q, *J* = 273.3 Hz), 121.6, 123.7 (q, *J* = 34.7 Hz), 127.4, 127.7, 128.3, 128.4, 129.4, 131.9, 138.6 ; ^{19}F NMR ($CDCl_3$) ! = –66.83 (s, 3F); IR (neat) ! 3034, 2986, 2935, 2201, 1589, 1491, 1389, 1292, 1183, 1139, 1030, 867, 756, 689 cm^{-1}; HRMS calcd for $C_{23}H_{18}F_3O$ (M+) 367.1310, found 367.1312.

*4.4.11. (E)-3-(Difluoromethyl)-1,6-diphenylhex3-en-1,5-diyne (**8Aa**)*

Yield: 74% (*E:Z* = 92:8); ^{1}H NMR ($CDCl_3$) ! 6.21 (t, *J* = 55.8 Hz, 1H), 6.43 (t, *J* = 2.4 Hz, 1H), 7.35 – 7.38 (m, 6H), 7.52 – 7.57 (m, 4H); ^{13}C NMR ($CDCl_3$) ! 82.9 (t, *J* = 4.2 Hz), 85.8, 99.9, 101.0 (t, *J* = 2.5 Hz), 112.7 (t, *J* = 240.8 Hz), 119.1 (t, *J* = 9.1 Hz), 122.2, 122.4, 127.0 (t, *J* = 22.7 Hz), 124.5, 128.5, 129.2, 129.3, 131.87, 131.90; ^{19}F NMR ($CDCl_3$) ! ! 116.17 (d, *J* = 53.4 Hz, 2F, *Z*-isomer), ! 114.64 (d, *J* = 55.8 Hz, 2F, *E*-isomer); IR (neat) ! 3061, 2867, 2214, 1955, 1683, 1598, 1491, 1402, 1048, 917, 895 cm^{-1}; HRMS calcd for $C_{19}H_{12}F_2$ (M+) 278.0907, found 278.0909.

*4.4.12. (E)-5,5,6,6,7,7-Hexafluoro-1-phenyl-4-(phenylethynyl)hept-3-en-1-yne (**9Aa**)*

Yield: 44% (*E:Z* = 94:6); ^{1}H NMR ($CDCl_3$) ! 6.12 (tt, *J* = 52.0, 5.6 Hz, 1H), 6.60 (s, 1H), 7.35 – 7.42 (m, 6H), 7.54 (m, 4H); ^{13}C NMR ($CDCl_3$) ! 82.3 (t, *J* = 5.0 Hz), 85.7, 100.9, 103.3 (t, *J* = 1.7 Hz), 108.9 (tt, *J* = 253.3, 31.4 Hz), 100 – 130 (m, 2C), 121.97, 122.09 (t, *J* = 25.6 Hz), 122.14, 122.6 (t, *J* = 8.7 Hz), 128.5, 128.6, 129.5, 129.6, 131.8, 132.0; ^{19}F NMR ($CDCl_3$) ! ! 137.15 (dquint., *J* = 52.0, 7.3 Hz, 2F), ! 130.31 (q, *J* = 6.5 Hz, 2F), ! 112.60 (t, *J* = 7.3 Hz, 2F); IR (neat) ! 3517, 3056, 2189, 1491, 1357, 1205, 1154, 1014, 916, 862 cm^{-1}; HRMS calcd for $C_{21}H_{12}F_6$ (M+) 378.0843, found 378.0846.

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[12] Assignment of the stereochemistry of **3a** was made by NMR spectroscopy. The coupling constant between vicinal H and F ($^3J_{H\text{-}F}$) of **3a** was 28.8 Hz, which indicates the **3a** possesses *Z* configuration. The stereochemistries of the other enynes were determined on the basis of the vicinal H-F coupling constants.