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Diastereoselective formation of 2-fluoro-2-trifluoromethyl-3,4-alkadienamides from propargyl alcohols and hexafluoropropene–diethylamine adduct (PPDA)☆

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Abstract

Treatment of propargyl alcohols (**1**) with hexafluoropropene–diethylamine adduct (PPDA) affords *N*,*N*-diethyl-2-fluoro-2-trifluoromethyl-3,4-alkadienamides (**2**) that are produced by the Claisen rearrangement of intermediary 2-alkynyl 1-(*N*,*N*-diethylamino)-2,3,3,3-tetrafluoro-1-propenyl ethers. Starting from propargyl alcohols bearing a triple bond at the terminal position, the corresponding products (**2**) were formed with a high stereoselectivity.

Keywords: Hexafluoropropene–diethylamine adduct (PPDA); Propargyl alcohol; *N*,*N*-Diethyl-2-fluoro-2-trifluoromethyl-3,4-alkadienamide; [3,3] Sigmatropic rearrangement

1. Introduction

Allenes are notable because they have a cumulative double bond that is axially chiral. Some kinds of allenes are known to be naturally occurring products that are biologically active: for example, pyretholone [1], mycomycine [2], long chain $\Delta^{9,10}$-allenes [3], and methyl (*E*)-(−)-2,4,5-tetradecatrienoate [4]. Since various fluorine compounds are known to possess unique biological properties [5], fluorine-containing allenes are very interesting from a viewpoint of developing novel biologically active compounds. Indeed, there have been many papers on their preparation [6]. To our surprise, only one compound that contains perfluoroethylidene [$F(CF_3)C<$] moiety is known in the literature [7]. Here, we wish to report a novel route leading to *N*,*N*-diethyl-2-fluoro-2-trifluoromethyl-3,4-alkadienamides. Since the allenes are valuable as synthetic precursors in the field of organic synthesis [8], various methods for preparing from acetylene derivatives were reported. Typical reaction paths are summarized in Scheme 1. An addition and elimination reaction (Eq. (1) [9] and Eq. (1′) [10]) [2,3], Wittig rearrangement (Eq. (2)) [11], and [3,3] sigmatropic rearrangements (Eq. (3)) [12].

During our investigation to utilize hexafluoropropene–diethylamine adduct (PPDA) as a synthetic reagent of α-fluoro-α-trifluoromethyl carbonyl compounds, this reagent was found to react with allylic alcohols (**I**) to give 2-fluoro-2-trifluoromethyl 4,5-alkenamides (**II**) in Scheme 2(a).

This reaction occurs via the [3,3] sigmatropic rearrangement of an intermediary 1-(*N*,*N*-diethylamino)ethenyl 2-alken-1-yl ether (**III**) [13]. If a propargyl alcohol (**I′**) is employed instead of the allylic alcohol, the corresponding allenamide (**II′**) would be formed as shown in Scheme 2(b). Hence, we initiated to investigate the reaction of propargyl alcohols with PPDA. In this report, we describe the diastereoselective formation of *N*,*N*-diethyl-2-fluoro-2-trifluoromethyl-3,4-alkadienamides in the reaction of propargyl alcohols with PPDA (Scheme 3).

2. Results and discussion

In the reaction of allylic alcohols with PPDA, the best result was obtained when 1.5–2 mol eq. of PPDA was used in dry chloroform. First, these reaction conditions were applied to the reaction of propargyl alcohols (**1**). To our delight, the reaction proceeded smoothly at room temperature to afford the expected 2-fluoro-2-trifluoromethyl-3,4-

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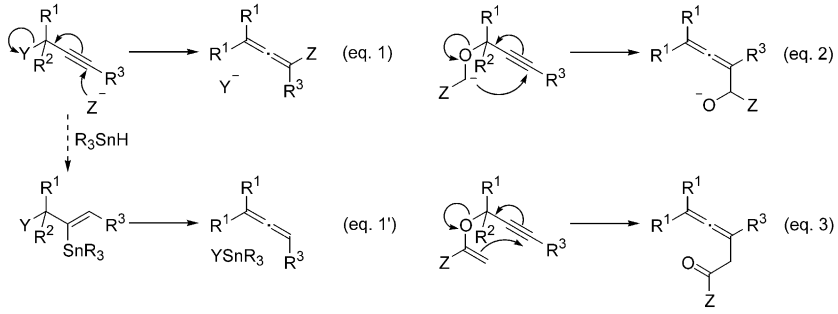
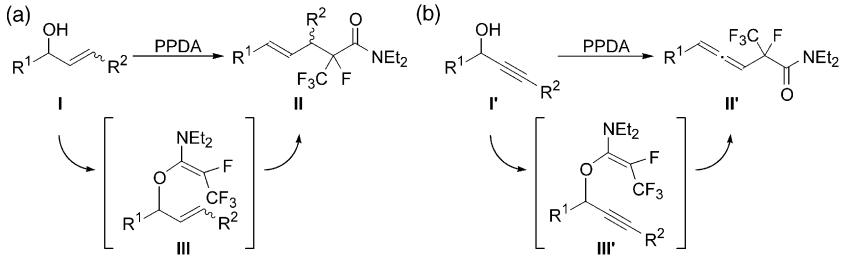


Scheme 1.

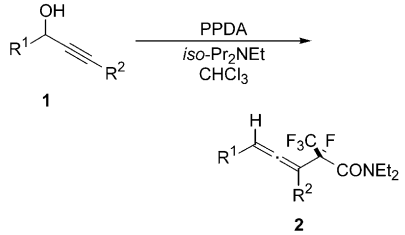


Scheme 2.

alkadienamides (**2**) from 2-alkyn-1-ols (**1a**–**d**) and 1-alkyn-3-ols (**1e**–**h**).

The results were summarized in Table 1, informing that the yield of **2** is higher with 2 mol eq. of PPDA and the reaction completes usually within 2 days, except for the case that a large group is substituted in the propargyl alcohol (entry 9 in Table 1).

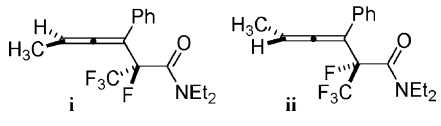
In the reaction of 1-alkyn-3-ols (**1e**–**h**) in which R^1 is not hydrogen, two diastereomers would be produced because the products have two chiral centers based on allene and perfluoroethylidene moieties. As being apparent from entries 7 to 10 in Table 1, the reaction proceeded with a high diastereoselectivity. The present reaction conditions are tolerable to the transformation of various propargyl alcohols bearing an acid-sensitive functionality. Thus, the propargyl alcohols bearing a vinyl moiety, a thioether linkage or an ether linkage (**1i**, **1j**, or **1k**, respectively) could be converted to the corresponding 2-fluoro-2-trifluoromethyl-3,4-alkadienamides (**2**) as summarized in Table 2. The structures of **2** were assigned from their satisfactory physical data (^{1}H NMR, IR, and elemental analysis) that are given in Section 4.



Scheme 3.

It is a problem to assign the diastereomeric structure of **2** ($R^1 \neq H$). As the mentioned above, the reaction of **1** ($R^1 \neq H$) with PPDA afforded two diastereomers. Fortunately, we could obtain single crystals of the major diastereomer of **2h** that have good quality suitable to single-crystal X-ray crystallographic analysis. The crystallographic details of **2h** are shown in Table 3 and Fig. 1.

Fig. 1 depicted the molecules of **2h** in a crystalline state. Interestingly, a pair of the enantiomers of **2h** contact one another through CH-π interaction between the phenyl ring and *N*-ethyl hydrogen. Intermolecular distances of H(29)–C(19), H(29)–C(27), H(32)–C(18), H(32)–C(21), and H(41B)–C(37) are 2.91, 2.93, 2.86, 2.94, and 2.95 Å, respectively. They are enough short to interact each other through CH-π interaction [14]. Interestingly, intramolecular hydrogen bonds between fluorine atom and the hydrogen of *N*,*N*-diethylamino group or phenyl ring are also observed: interatomic distances of F(1)–H(22), F(1)–H(28A), F(1)–H(40C), F(2)–H(27) and F(2)–H(38A) are 2.31, 2.42, 2.55, 2.47, and 2.19 Å, respectively. It should be noted that the stereochemical relationship between two chiral centers in the major diastereomer of **2h** was depicted as the structures (**i**) and (**ii**), based on the "zig-zag conformation" that is proposed by Hoppe for the description of allene stereochemistry [15].



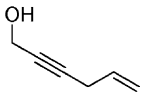
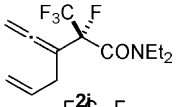
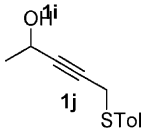
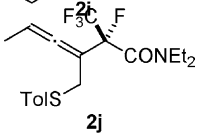
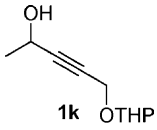
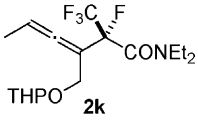
In this conformation, methyl and trifluoromethyl groups are located with an "anti" relationship. Therefore, it is

Table 1
Formation of **2** from propargyl alcohols

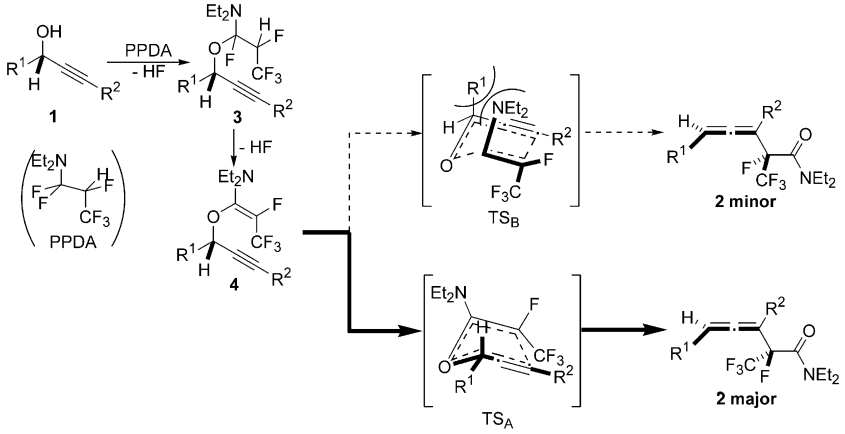
Entry	**1**	R^1	R^2	PPDA (eq.)	*iso*-Pr_2NEt (eq.)	Time (h)	Product	Yield (%)[a]
1	**a**	H	H	1.5	4.5	36	**2a**	82
2				2.0	6.0	33		88
3	**b**	H	CH_3	1.5	4.5	23	**2b**	81
4				2.0	6.0	23		82
5	**c**	H	C_2H_5	2.0	6.0	36	**2c**	85
6	**d**	H	Ph	2.0	6.0	48	**2d**	81
7	**e**	CH_3	H	2.0	6.0	23	**2e**	70 (94:6)[b]
8	**f**	C_2H_5	H	2.0	6.0	40	**2f**	82 (92:8)[c]
9	**g**	*n*-C_5H_{11}	H	2.0	6.0	64	**2g**	68 (96:4)[c]
10	**h**	Me	Ph	3.0[d]	6.0	40	**2h**	70 (94:6)[b]

[a] Isolated yield. The value in the parentheses is a diastereomeric ratio of the product.
[b] The diastereomeric ratio was determined by ^1H NMR.
[c] The diastereomeric ratio was determined by HPLC.
[d] 1.0 mol eq. of PPDA was added after 15 h passed.

Table 2
Formation of **2** from miscellaneous propargyl alcohols[a]

Entry	**1**	PPDA (eq.)	$^iPr_2NEt$ (eq.)	Time (h)	**2**	Yield (%)[b]
1	 **1i**	1.5	4.5	29	 **2i**	75
2	 **1j**	2.0	6.0	38	 **2j**	92[c]
3	 **1k**	2.0	6.0	47	 **2k**	67[c]

[a] These reactions were performed at room temperature.
[b] Isolated yield.
[c] The diastereomeric ratio could not be determined.

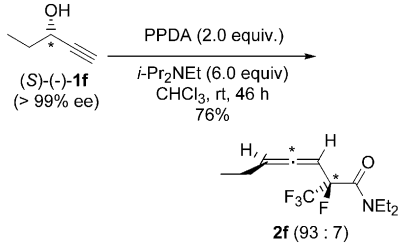


Scheme 4.

Table 3
Crystallographic details for **2h**

Empirical formula	$C_{17}H_{19}F_4N$
M_w	329.30
Crystal size	0.6 mm × 0.4 mm × 0.4 mm
Crystal system	Monoclinic
Space group	$P2_1/n$
Z	8
Unit cell dimensions	
a (Å)	19.513 (4)
b (Å)	12.773 (2)
c (Å)	14.323 (4)
α (°)	90.000 (0)
β (°)	107.72 (2)
γ (°)	90.000 (0)
V (Å^3)	3400 (1)
μ (mm^{-1})	9.433
D_{cale} (g cm^{-3})	1.286
λ (Å)	1.5415 (Cu Kα)
T (K)	298
Index ranges	
h	$-23 \le h \le 22$
k	$-15 \le k \le 0$
l	$0 \le l \le 17$
Scan technique	$\theta/2\theta$
θ range	$28.26 \le \theta \le 29.93$
Number of total reflections	7278
Number of unique reflections	6464
Number of observed reflections	3008
Number of parameters	453
Criteria of I	$I \le 2\sigma(I)$
Use of F, F^2 or I	F
R_{int}	0.050
GOF	3.619
R (F)	0.071
wR (F)	0.069
$\Delta\rho_{max,min}$ (e Å^{-3})	0.32, −0.28

reasonably assumed that the major diastereomer of **2** derived from **1** ($R^1 \neq H$) has ''anti'' configuration between the allene and the perfluoroethylidene moieties.



Scheme 5.

Although at this point no rigorous mechanistic studies have been conducted, a working hypothesis has evolved based on the observed products and the known behavior of allylic alcohols toward PPDA. Presumably, the formation of **2** from **1** proceeds via the [3,3] sigmatropic rearrangement (the Claisen rearrangement) of 2-alkynyl 1-(*N*,*N*-diethylamino)-2,3,3,3-tetrafluoro-1-propenyl ether (**4**) that is the key intermediate (Scheme 4). The intermediate (**4**) is formed by dehydrofluorination of the primary intermediate, that is, 2-alkynyl 1-(*N*,*N*-diethylamino)-2,2,3,3,3-pentafluoro-1-propanyl ether (**3**). According to the semiempirical MO calculation (MNDO/PM3), the favorable regioisomerism of the enamine moiety of **4** is *E* [16]. For the transition state of the [3,3] sigmatropic rearrangement, two conformers (TS_A and TS_B) in Scheme 4 are possible. In the transition state (TS_B), the 1,3-diaxial repulsive interaction between the diethylamino group and the alkyl substituent (R^1) exists. As a result, the transition state (TS_A) seems to be preferable in the conversion of **4**–**2**. This is in accordance with the fact that the major diastereomer has ''anti'' configuration.

This mechanism implies that the chiral center of **1** can be transferred into the chiral allene and perfluoroethylidene moiety of **2**. Hence, we prepared (*S*)-**1f** with an enantiomeric excess of more than 99% according to the literature [17]. In the reaction with PPDA, (*S*)-**1f** gave the corresponding **2** in 76% yield with a diastereomeric ratio of 93:7. Two diastereomers were separated by a preparative HPLC and

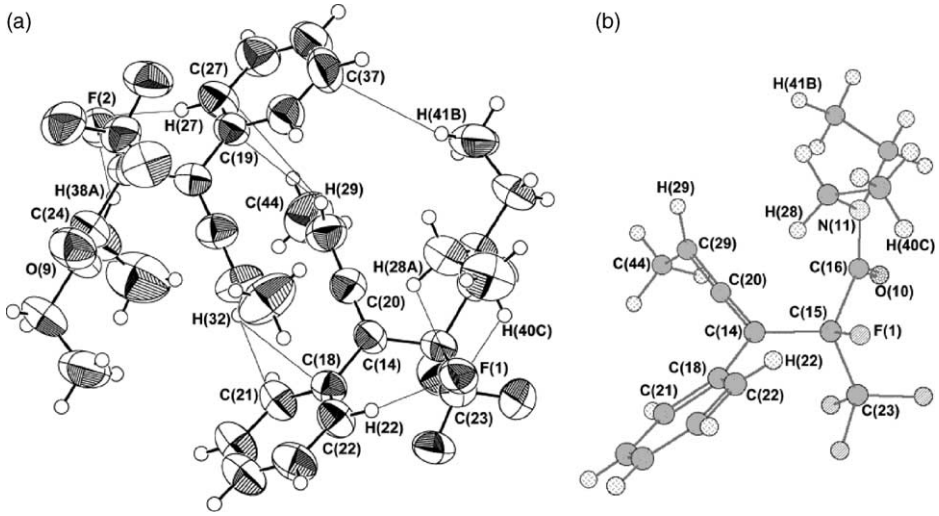


Fig. 1. (a) ORTEP drawing for inter- and intramolecular close contacts of racemic compound **2h**. (b) Chem3D® description of one molecule of **2h**.

their enantiomeric excesses were determined by the use of a chiral shift reagent Eu(hfc)$_3$ (europium tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate]) [18] exhibiting that both of the diastereomers are essentially enantiomerically pure (more than 99% ee) (Scheme 5). Therefore, the conversion path from **1** to **2** was shown to be kinetically controlled and, as a result, stereospecific.

3. Conclusion

In conclusion, the reaction of propargyl alcohols (**1**) with PPDA in the presence of *N*,*N*-diisopropylethylamine affords *N*,*N*-diethyl-2-fluoro-2-trifluoromethyl-3,4-alkadienamides (**2**). The reaction of **1** with PPDA involves [3,3] sigmatropic rearrangement of intermediary 2-alkynyl 1-(*N*,*N*-diethylamino)-2,3,3,3-tetrafluoro-1-propenyl ether. It is intriguing that 1-alkyn-3-ols was subject to the reaction in high diastereomeric manner. This reaction is expected to open a new way for developing novel fluorine-containing building blocks and biologically active compounds.

4. Experimental

4.1. Materials

The material used herein were obtained from commercial suppliers (Aldrich, Tokyo Kasei Chemical Industry Co. Ltd., Wako Pure Chemical Co. Ltd., Kanto Chemical Co. Inc., Nakarai Tesque Co. Inc.). PPDA was supplied from Tokyo Kasei Co. Ltd. This reagent is the mixture of diethylperfluoropropylamine (hexafluoropropene–diethylamine adduct, PPDA) and diethylperfluoropropenylamine and their ratio was assumed to be 3:1 according to Ishikawa's report [19].

4.2. Instrumentations

Kugelrohr micro distillation was performed with GTO-250RS glass tube oven. Infrared spectra were recorded with JASC0-FT/IR-350. ^{1}H and ^{13}C NMR spectra were recorded on Varian GEMINI-2000 (300 and 75 MHz, respectively). ^{19}F NMR spectra were recorded on HITHACHI R-90H (84.7 MHz) using trifluoroacetic acid as an external standard. Microanalytical data were provided by the Analysis Center of Chiba University. Fast atom bombardment mass spectrum (FABMS) and electron ionization mass spectrum (EIMS) were recorded with JOEL JMS HX-110A and JMS 700T spectrometer, respectively. Analytical HPLC was performed on HITACHI L-6000 equipped with L-4000 UV detector or JASCO PU-980 equipped with UV-970 UV detector. Preparative HPLC was performed on LC-908 (Japan Analytical Industry Co. Ltd.). Optical rotations were measured on JASCO DIP-370 at 25 °C (cell: diameter 3.5 mm × length 100 mm). X-ray crystallographic analysis was performed on MAC Science MXC 18 diffractometer.

4.3. Procedure of the reaction of propargylic alcohol (*1a*) with PPDA in the presence of *N*,*N*-diisopropylethylamine

To a solution of propargyl alcohol (**1a**) (393 mg, 7.0 mmol) and *N*,*N*-diisopropylethylamine (7.4 ml, 42 mmol) in dry chloroform (7 ml), was dropwise added a solution of hexafluoropropene–diethylamine adduct (2.48 ml, 14 mmol) in dry chloroform (7 ml) over 9 min at room temperature. The resulting mixture was stirred for 33 h at room temperature and then quenched with water (10 ml). The aqueous layer was extracted by chloroform (3 × 10 ml). The combined organic layers were washed with 1N hydrochloric acid (3 × 20 ml), saturated aqueous solution of $NaHCO_3$ (1 × 10 ml), and brine (2 × 10 ml). The organic layer was dried over $MgSO_4$ and evaporated in vacuo to give an orange oil (2.99 g). The orange oil was chromatographed on silica gel [eluent: *n*-hexane–ethyl acetate (10:1)] to give *N*,*N*-diethyl-2-fluoro-2-trifluoromethyl-3,4-pentadienamide (**2a**) as a colorless oil (1.47 g: 88% yield). Compound **2a** was further purified by Kugelrohr distillation.

4.3.1. *N*,*N*-Diethyl-2-fluoro-2-trifluoromethyl-3,4-pentadienamide (*2a*)

A colorless oil: bp 116 °C/4 mmHg; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.15 (t, 3H, J = 7.1 Hz, $CON(CH_2CH_3)$), 1.21 (t, 3H, J = 7.0 Hz, $CON(CH_2CH_3)$), 3.13–3.30 (m, 2H, $CON(CH_2CH_3)$ or $CON(CH(H)CH_3)(CH(H)CH_3)$), 3.70–3.52 (m, 2H, $CON(CH_2CH_3)$ or $CON(CH(H)CH_3)(CH(H)CH_3)$), 5.13 (dd, 1H, J = 12.8, 6.3 Hz, C*H*(H)=C=CHCF), 5.16 (ddd, 1H, J = 12.8, 6.6, 5.2 Hz, CH(*H*)=C=CHCF), 5.58 (ddd, 1H, J = 13.3, 6.7, 6.7 Hz, CH_2=C=C*H*CF); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.8 ($CON(CH_2CH_3)$), 15.0 (d, J = 2.8 Hz, $FCCON(CH_2CH_3)$), 42.4 ($CON(CH_2CH_3)$), 43.0 (d, J = 11.4 Hz, FCCON-(CH_2CH_3)), 81.5 (CH_2=C=CHCF), 86.6 (d, J = 25.4 Hz, C=CHCF), 93.1 (dq, J = 205.9, 29.6 Hz, F_3CCF), 122.7 (qd, J = 285.2, 31.4 Hz, F_3CCF), 162.7 (d, J = 20.2 Hz, FC*C*ON), 209.9 (d, J = 9.2 Hz, CH_2=*C*=CHCF); IR (neat) 2982, 2941, 1982, 1956, 1663, 1438, 1287, 1212, 1169, 1053, 970, 855 cm^{-1}. Anal. Calcd. for $C_{10}H_{13}F_4NO$: C, 50.21; H, 5.48; N, 5.86. Found: C, 50.27; H, 5.65; N, 5.80.

4.4. The reaction of 2-alkyn-1-ols with PPDA in the presence of *N*,*N*-diisopropylethylamine: a typical procedure

To a solution of 2-pentyn-1-ol (**1c**) (841 mg, 10 mmol) and *N*,*N*-diisopropylethylamine (10.5 ml, 60 mmol) in dry chloroform (10 ml), was dropwise added PPDA (3.5 ml, 20 mmol) in dry chloroform (10 ml) at room temperature over 17 min. Then, the solution was stirred at room temperature for 36 h, quenched with water (10 ml), and extracted with ether (4 × 10 ml). The combined organic layers were washed with 1N hydrochloric acid (3 × 20 ml) and brine (2 × 20 ml). The organic layer was dried over $MgSO_4$ and evaporated in vacuo to give a yellow oil (4.31 g). The oil was chromatographed on silica gel [eluent:

n-hexane–ethyl acetate (8:1)] to give *N,N*-diethyl-3-ethyl-2-fluoro-2-trifluoromethyl-3,4-pentadienamide (**2c**) as a colorless oil (2.28 g: 85% yield). Compound **2c** was further purified by Kugelrohr distillation.

4.4.1. N,N-Diethyl-2-fluoro-3-ethyl-2-trifluoromethyl-3,4-pentadienamide (*2c*)

A colorless oil: bp 114 °C/3 mmHg; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.06 (t, 3H, $J = 7.3$ Hz, C=CCH$_2$CH_3), 1.14 (t, 3H, $J = 7.1$ Hz, CON(CH$_2$CH_3)), 1.19 (t, 3H, $J = 7.1$ Hz, CON(CH$_2$CH_3)), 2.29–2.00 (m, 2H, CH$_2$=C=C(CH_2)CF), 3.05–3.19 (m, 2H, CON(CH_2CH$_3$) or CON(C*H*(H)CH$_3$)-(C*H*(H)CH$_3$)), 3.48–3.72 (m, 2H, CON(CH_2CH$_3$) or CON(C*H*(H)CH$_3$)(C*H*(H)CH$_3$)), 5.04–5.21 (m, 2H, CH_2=C=C(CH$_2$)CF); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.4 (C=CCH$_2$*C*H$_3$), 12.5 (CON(CH$_2$*C*H$_3$)), 14.6 (CON(CH$_2$-*C*H$_3$)), 19.7 (C=C*C*H$_2$CH$_3$), 41.8 (CON(*C*H$_2$CH$_3$)), 42.5 (d, $J = 9.2$ Hz, FCCON(*C*H$_2$CH$_3$)), 82.6 (*C*H$_2$=C=C), 94.4 (dq, $J = 205.7$, 28.9 Hz, F$_3$*C*CF), 100.9 (d, $J = 23.4$ Hz, C=*C*CF), 123.0 (qd, $J = 285.9$, 32.2 Hz, F$_3$*C*CF), 163.0 (d, $J = 20.0$ Hz, FC*C*ON), 207.6 (d, $J = 7.6$ Hz, CH$_2$=*C*=CCF); IR (neat) 2977, 2940, 1955, 1663, 1437, 1293, 1208, 1165, 1063, 1029, 943, 706 cm^{-1}. Anal. Calcd. for $C_{12}H_{17}F_4NO$: C, 53.93; H, 6.41; N, 5.24. Found: C, 54.12; H, 6.17; N, 5.08.

4.4.2. N,N-Diethyl-2-fluoro-3-methyl-2-trifluoromethyl-3,4-pentadienamide (*2b*)

A colorless oil: bp 93 °C/5 mmHg (short path distillation); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.14 (t, 3H, $J = 7.0$ Hz, CON(CH$_2$CH_3)), 1.20 (t, 3H, $J = 7.0$ Hz, CON(CH$_2$CH_3)), 1.87 (m, 3H, CH$_2$=C=C(CH_3)CF), 3.04–3.20 (m, 2H, CON(CH_2CH$_3$) or CON(C*H*(H)-CH$_3$)(C*H*(H)CH$_3$)), 3.51–3.72 (m, 2H, CON(CH_2CH$_3$) or CON(C*H*(H)CH$_3$)(C*H*(H)CH$_3$), 4.97 (ddq, 1H, $J = 12.0$, 3.5, 3.3 Hz, C*H*(H)=C=C(CH$_3$)CF), 5.05 (ddq, 1H, $J = 12.0$, 3.2, 3.0 Hz, CH(*H*)=C=C(CH$_3$)CF); IR (neat) 2979, 2940, 1959, 1662, 1435, 1384, 1295, 1207, 1166, 1038, 1011, 836 cm^{-1}. Anal. Calcd. for $C_{11}H_{15}F_4NO$: C, 52.17; H, 5.97; N, 5.53. Found: C, 51.89; H, 5.91; N, 5.53.

4.4.3. N,N-Diethyl-2-fluoro-3-phenyl-2-trifluoromethyl-3,4-pentadienamide (*2d*)

A colorless solid: mp 32–33 °C (decomposition 165 °C/4 mmHg); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.98 (t, 3H, $J = 7.1$ Hz, CON(CH$_2$CH_3)), 1.18 (t, 3H, $J = 7.1$ Hz, CON(CH$_2$CH_3)), 2.96–3.20 (m, 2H, CON(CH_2CH$_3$) or CON(C*H*(H)CH$_3$)(C*H*(H)CH$_3$)), 3.56–3.75 (2H, m, CON(CH_2CH$_3$) or CON(C*H*(H)CH$_3$)(C*H*(H)CH$_3$)), 5.28 (dd, 1H, $J = 13.3$, 5.5 Hz, C*H*(H)=C=CCF), 5.35 (dd, 1H, $J = 13.3$, 4.8 Hz, CH(*H*)=C=CCF), 7.29–7.45 (m, 5H, Ar-*H*); IR (neat) 2980, 1966, 1941, 1666, 1447, 1288, 1204, 1173, 1082, 1032, 876, 698 cm^{-1}. Anal. Calcd. for $C_{16}H_{17}F_4NO$: C, 60.95; H, 5.43; N, 4.44. Found: C, 61.15; H, 5.24; N, 4.47.

4.5. The reaction of 1-alkyn-3-ols with PPDA in the presence of N,N-diisopropylethylamine: a typical procedure

To a solution of 1-butyn-3-ol (**1e**) (561 mg, 8.0 mmol) and *N,N*-diisopropylethylamine (6.3 ml, 36 mmol) in dry chloroform (8 ml), was dropwise added a solution of PPDA (2.1 ml, 12 mmol) in dry chloroform (6 ml) over 15 min at room temperature. The resulting solution was stirred for 23 h at room temperature and quenched with water (10 ml). The aqueous layer was separated and extracted by ether (4×10 ml). The combined organic layers were washed with 1N hydrochloric acid (5×10 ml) and brine (2×20 ml). The resulting organic layer was dried over $MgSO_4$ and evaporated in vacuo to give an orange oil (2.49 g) that was chromatographed on silica gel [eluent: *n*-hexane–ethyl acetate (8:1)] to give *N,N*-diethyl-2-fluoro-2-trifluoromethyl-3,4-hexadienamide (**2e**) (709 mg: 70% yield) as a diastereomeric mixture. The diastereomeric ratio of **2e** was determined by ^{1}H NMR to be 94:6. The separation of two diastereomers (**2e** major, **2e** minor) was achieved by preparative HPLC [YMC pack 60A: eluent; *n*-hexane–ethyl acetate (2:1)]. Finally, these diastereomers were purified by Kugelrohr distillation.

4.5.1. N,N-Diethyl-2-fluoro-2-trifluoromethyl-3,4-hexadienamide (*2e*)

*4.5.1.1. The major diastereomer of **2e**.* A colorless oil: bp 99 °C/2.5 mmHg; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.13 (t, 3H, $J = 7.1$ Hz, CON(CH$_2$CH_3)), 1.20 (t, 3H, $J = 7.0$ Hz, CON(CH$_2$CH_3)), 1.72 (dd, 3H, $J = 7.1$, 3.5 Hz, CH_3CH=C=CH), 3.07–3.24 (m, 2H, CON(CH_2CH$_3$) or CON(C*H*-(H)CH$_3$)(C*H*(H)CH$_3$)), 3.57–3.72 (m, 2H, CON(CH_2CH$_3$) or CON(C*H*(H)CH$_3$)(C*H*(H)CH$_3$)), 5.42–5.56 (m, 2H, CH$_3$C*H*=C=C*H*CF); ^{19}F NMR (84.7 MHz, $CDCl_3$, external standard CF_3COOH) δ −83.28 (m, 1F, CF$_3$C*F*), 1.57 (d, 3F, $J = 6.2$ Hz, C*F*$_3$CF); IR (neat) 2981, 1969, 1666, 1464, 1450, 1286, 1211, 1168, 1065, 1022, 972, 852 cm^{-1}. Anal. Calcd. for $C_{11}H_{15}F_4NO$: C, 52.17; H, 5.97; N, 5.53. Found: C, 52.01; H, 5.86; N, 5.41.

*4.5.1.2. The minor diastereomer of **2e**.* A colorless oil: bp 86 °C/7 mmHg; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.14 (t, 3H, $J = 7.1$ Hz, CON(CH$_2$CH_3)), 1.21 (t, 3H, $J = 7.0$ Hz, CON(CH$_2$CH_3)), 1.73 (dd, 3H, $J = 7.3$, 3.3 Hz, CH_3CH=C=CH), 3.05–3.20 (m, 2H, CON(CH_2CH$_3$) or CON(C*H*-(H)CH$_3$)(C*H*(H)CH$_3$)), 3.60–3.80 (m, 2H, CON(CH_2CH$_3$) or CON(C*H*(H)CH$_3$)(C*H*(H)CH$_3$)), 5.48 (ddq, 1H, $J = 15.4$, 6.4, 3.1 Hz, CH$_3$CH=C=C*H*CF), 5.51–5.62 (m, 1H, CH$_3$C*H*=C=CHCF); ^{19}F NMR (84.7 MHz, $CDCl_3$, external standard CF_3COOH) δ −82.65 (m, 1F, CF$_3$C*F*), 1.60 (d, 3F, $J = 6.2$ Hz, C*F*$_3$CF); IR (neat) 2981, 1973, 1666, 1450, 1437, 1302, 1286, 1211, 1169, 1066, 1022, 972 cm^{-1}. Anal. Calcd. for $C_{11}H_{15}F_4NO$: C, 52.17; H, 5.97; N, 5.53. Found: C, 52.31; H, 5.95; N, 5.64.

*4.5.2. N,N-Diethyl-2-fluoro-2-trifluoromethyl-3,4-heptadienamide (**2f**)*

The diastereomeric ratio was 92:8 [by YMC Pack 60A-equipped HPLC; *n*-hexane–ethyl acetate (8:1)]. The diastereomers were separated by HPLC [YMC pack 60A: eluent; *n*-hexane–ethyl acetate (6:1)]. Finally these diastereomers were purified by Kugelrohr distillation.

*4.5.2.1. The major diastereomer of **2f**.* A colorless oil: bp 99 °C/4 mmHg; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.02 (t, 3H, $J = 7.1$ Hz, CH_3CH$_2$CH), 1.13 (t, 3H, $J = 7.1$ Hz, CON(CH$_2$CH_3)), 1.20 (t, 3H, $J = 6.9$ Hz, CON(CH$_2$CH_3)), 2.07 (qdd, 2H, $J = 7.3$, 6.8, 3.2 Hz, CH$_3$CH_2CH=C=CH), 3.06–3.22 (m, 2H, CON(CH_2CH$_3$) or CON(CH(H)CH$_3$)(CH(H)CH$_3$)), 3.52–3.75 (m, 2H, CON(CH_2CH$_3$) or CON(CH(H)CH$_3$)(CH(H)CH$_3$)), 5.53 (ddt, 1H, $J = 14.8$, 6.5, 3.4 Hz, CH=C=CHCF), 5.52–5.67 (m, 1H, CH$_2$CH=C=CH); IR (neat) 2975, 1971, 1666, 1464, 1450, 1437, 1286, 1211, 1167, 1056, 1024, 851 cm^{-1}. Anal. Calcd. for $C_{12}H_{17}F_4NO{\cdot}0.3H_2O$: C, 52.86; H, 6.51; N, 5.14. Found: C, 53.01; H, 6.29; N, 5.13. LRMS (EI, 70 eV) 267 (M^+, 8.76%), 252 (3.87%), 248 (3.89%), 198 (100%), 100 (13.6%), 72 (18.9%).

*4.5.2.2. The minor diastereomer of **2f**.* A colorless oil (hygroscopic): bp 108 °C/6 mmHg; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.05 (t, 3H, $J = 7.4$ Hz, CH_3CH$_2$CH), 1.15 (t, 3H, $J = 7.1$ Hz, CON(CH$_2$CH_3)), 1.21 (t, 3H, $J = 6.9$ Hz, CON(CH$_2$CH_3)), 2.04–2.15 (m, 2H, CH$_3$CH_2CH), 3.11–3.24 (m, 2H, CON(CH_2CH$_3$) or CON(CH(H)CH$_3$)(CH(H)CH$_3$)), 3.52–3.75 (m, 2H, CON(CH_2CH$_3$) or CON(CH(H)CH$_3$)(CH(H)CH$_3$)), 5.53 (ddt, 1H, $J = 13.4$, 6.5, 3.3 Hz, CH$_2$CH=C=CHCF), 5.65 (dtd, 1H, $J = 6.5$, 6.3, 4.4 Hz, CH$_2$CH=C=CH); IR (neat) 2976, 1970, 1666, 1450, 1436, 1296, 1286, 1211, 1169, 1054, 1024, 970 cm^{-1}. Anal. Calcd. for $C_{12}H_{17}F_4NO{\cdot}0.2H_2O$: C, 53.21; H, 6.47; N, 5.17. Found: C, 53.24; H, 6.75; N, 5.05. LRMS (EI, 70 eV) 267 (M^+, 17.2%), 252 (5.35%), 248 (4.81%), 198 (100%), 100 (15.5%), 72 (22.6%).

*4.5.3. N,N-Diethyl-2-fluoro-2-trifluoromethyl-3,4-decadienamide (**2g**)*

The diastereomeric ratio of **2g** was determined to be 96:4 [by YMC Pack 60A-HPLC; *n*-hexane–ethyl acetate (16:1)]. The diastereomers were separated by HPLC [YMC pack 60A: eluent; *n*-hexane–ethyl acetate (6:1)]. Finally these diastereomers were purified by Kugelrohr distillation.

*4.5.3.1. The major diastereomer of **2g**.* A colorless oil (hygroscopic): bp 117 °C/4 mmHg; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, 3H, $J = 6.7$ Hz, CH_3CH$_2$(CH$_2$)$_3$), 1.13 (t, 3H, $J = 7.1$ Hz, CON(CH$_2$CH_3)), 1.19 (t, 3H, $J = 7.1$ Hz, CON(CH$_2$CH_3)), 1.24–1.36 (m, 4H, CH$_3$(CH_2)$_2$CH$_2$CH$_2$), 1.36–1.49 (diffused quintet, 2H, CH$_2$CH_2CH$_2$CH=C), 2.05 (dtd, 2H, $J = 7.9$, 6.8, 3.3 Hz, CH$_2$CH_2CH=C), 3.09–3.28 (m, 2H, CON(CH_2CH$_3$) or CON(CH(H)CH$_3$)(CH(H)CH$_3$)), 3.50–3.74 (m, 2H, CON(CH_2CH$_3$) or CON(CH(H)CH$_3$)(CH(H)CH$_3$)), 5.46–5.63 (m, 2H, CH$_2$CH=C=CHCF); IR (neat) 2959, 2934, 1971, 1666, 1464, 1449, 1436, 1286, 1211, 1167, 1056, 1025 cm^{-1}. Anal. Calcd. for $C_{15}H_{23}F_4NO{\cdot}0.2H_2O$: C, 57.57; H, 7.54; N, 4.48. Found: C, 57.64; H, 7.55; N, 4.44. LRMS (EI, 70 eV) 309 (M^+, 7.69%), 290 (3.52%), 252 (18.0%), 240 (100%), 224 (4.16%), 183 (6.48%), 100 (24.7%), 72 (20.0%).

*4.5.3.2. The minor diastereomer of **2g**.* A colorless oil (hygroscopic): bp 118 °C/5 mmHg; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, 3H, $J = 6.8$ Hz, CH_3CH$_2$(CH$_2$)$_3$-CH=C), 1.14 (t, 3H, $J = 7.1$ Hz, CON(CH$_2$CH_3)), 1.21 (t, 3H, $J = 6.9$ Hz, CON(CH$_2$CH_3)), 1.26–1.36 (m, 4H, CH$_3$(CH_2)$_2$CH$_2$CH$_2$), 1.38–1.47 (m, 2H, CH$_2$CH_2CH$_2$-CH=C), 2.06 (dtd, 2H, $J = 7.2$, 7.2, 3.1 Hz, CH$_2$CH_2-CH=C), 3.10–3.23 (m, 2H, CON(CH_2HCH$_3$) or CON(CH(H)CH$_3$)(CH(H)CH$_3$)), 3.57 (dq, 1H, $J = 13.7$, 6.9 Hz, FCCON(CH(H)CH$_3$)(CH$_2$CH$_3$)), 3.61–3.75 (m, 1H, CON(CH(H)CH$_3$)), 5.50 (ddt, 1H, $J = 13.1$, 6.3, 3.2 Hz, CH$_2$CH=C=CHCF), 5.59 (dtd, 1H, $J = 6.7$, 6.7, 4.7 Hz, CH$_2$CH=C=CH); IR (neat) 2959, 2935, 1971, 1666, 1463, 1449, 1435, 1286, 1211, 1168, 1054, 1024 cm^{-1}. Anal. Calcd. for $C_{15}H_{23}F_4NO$: C, 58.24; H, 7.49; N, 4.53. Found: C, 57.94; H, 7.44; N, 4.41.

*4.5.4. The preparation of N,N-diethyl-2-fluoro-3-phenyl-2-trifluoromethyl-3,4-hexadienamide (**2h**)*

To a solution of 4-phenyl-3-butyn-2-ol (469 mg: purity 93.7 wt.%, 3.0 mmol) and *N*,*N*-diisopropylethylamine (3.14 ml, 18 mmol) in dry chloroform (3 ml), was dropwise added a solution of PPDA (1.06 ml, 5.8 mmol) in dry chloroform (3 ml) over 10 min at room temperature. After being stirred for 15 h at room temperature further, PPDA (0.53 ml, 3.0 mmol) in dry chloroform (3 ml) was dropwise added over 10 min to consume the unreacted starting material. The resulting solution was further stirred for 25 h and then quenched with water (10 ml). The aqueous layer was separated and extracted with ether (3 × 10 ml). The combined organic layers were washed with 1N hydrochloric acid (2 × 20 ml) and brine (2 × 20 ml), dried over $MgSO_4$, and evaporated in vacuo to give an orange oil containing colorless crystals (2.04 g). The residual mixture was chromatographed on silica gel [eluent: *n*-hexane–ethyl acetate (8:1)] to give *N*,*N*-diethyl-2-fluoro-2-trifluoromethyl-3,4-decadienamide (**2h**) (694 mg: 70% yield) as a diastereomeric mixture. The diastereomeric ratio of **2h** was determined by ^{1}H NMR to be 94:6.

*4.5.4.1. N,N-Diethyl-2-fluoro-3-phenyl-2-trifluoromethyl-3,4-hexadienamide (**2h**).* A colorless solid: mp 38–40 °C: ^{1}H NMR (300 MHz, $CDCl_3$) [major isomer]: δ 1.01 (t, 3H, $J = 7.1$ Hz, CON(CH$_2$CH_3)), 1.16 (t, 3H, $J = 7.0$ Hz, CON(CH$_2$CH_3)), 1.82 (d, 3H, $J = 7.3$ Hz, CH_3CH=C), 2.98–3.19 (m, 2H, CON(CH_2CH$_3$) or CON(CH(H)-

CH_3)(CH(H)CH_3)), 3.56–3.74 (m, 2H, CON(CH_2CH_3) or CON(CH(H)CH_3)(CH(H)CH_3)), 5.67 (dqd, 1H, $J = 7.2$, 7.2, 4.9 Hz, CH_3CH=C=CCF), 7.28–7.44 (m, 5H, Ph-*H*); [minor isomer]: δ 1.76 (d, $J = 7.3$ Hz, CH_3CH=C), 5.74 (dqd, $J = 7.4$, 7.4, 4.2 Hz, CH_3CH=C=CCF), The other signals are overlapped with signals of the major isomer; IR (KBr) 2981, 2930, 1957, 1662, 1459, 1436, 1295, 1293, 1179, 1083, 1024, 699 cm^{-1}. Anal. Calcd. for $C_{17}H_{19}F_4NO$: C, 62.00; H, 5.82; N, 4.25. Found: C, 61.77; H, 5.97; N, 4.16.

*4.5.4.2. X-ray crystallography of **2h** major.* Single crystals of **2h** major were obtained by recrystallization from *n*-hexane. X-ray crystallographic data were collected on a Mac Science MXC18 four-circle diffractometer with graphite monochromated Cu Kα ($\lambda = 1.5418$ Å) radiation using the $\theta/2\theta$ scan technique. The structure was solved by direct methods and refined by full-matrix least-squares methods against *F* (SIR 92 [20] on a computer program package; maXus version 1.1 from MAC Science Co. Ltd.). All non-hydrogen atoms were refined with anisotropic displacement parameters and hydrogen atoms refined isotropically. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication nos. CCDC219599 for **2h**. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CS2 1EZ, UK (fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

*4.6. The preparation of N,N-diethyl-2-fluoro-3-(2-propenyl)-2-trifluoromethyl-3,4-pentadienamide (**2i**)*

To a solution of 5-hexen-3-yn-1-ol (289 mg, 3.0 mmol) and *N*,*N*-diisopropylethylamine (2.4 ml, 14 mmol) in dry chloroform (3 ml), was dropwise added a solution of PPDA (797 μl, 4.5 mmol) in dry chloroform (4.6 ml) over 37 min at room temperature. The solution was stirred for 28 h at room temperature and then quenched with water (10 ml). The aqueous layer was separated and extracted with ether (4 × 10 ml). The combined organic layers were washed with 1N hydrochloric acid (3 × 10 ml) and brine (2 × 20 ml). The organic layer was dried over $MgSO_4$ and evaporated in vacuo to give a brown oil (990 mg). The residual oil was chromatographed on silica gel column [eluent: *n*-hexane–ethyl acetate (6:1)] to give *N*,*N*-diethyl-2-fluoro-3-(2-propenyl)-2-trifluoromethyl-3,4-decadienamide (**2i**) (625 mg: 75% yield). The diastereomeric ratio of **2i** could not be determined by ^{1}H NMR, because signals of the minor diastereomer was overlapped with signals of the major isomer.

*4.6.1. N,N-Diethyl-2-fluoro-3-(2-propenyl)-2-trifluoromethyl-3,4-pentadienamide (**2i**)*

A colorless oil: bp 118 °C/93 mmHg (Kugelrohr distillation); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.14 (t, 3H, $J = 7.1$ Hz, CON(CH_2CH_3), 1.19 (t, 3H, $J = 7.1$ Hz, CON(CH_2CH_3), 2.88 (m, 2H, C=C=C–CH_2–CH=C), 3.05–3.20 (m, 2H, CON(CH_2CH_3) or CON(CH(H)CH_3)(CH(H)CH_3)), 3.53–3.70 (m, 2H, CON(CH_2CH_3)(CH_2CH_3) or CON(CH(H)CH_3)(CH(H)CH_3)), 5.06–5.19 (m, 4H, CH_2=C=C and CH_2=CH–CH_2), 5.77 (ddt, 1H, $J = 17.1$, 10.0, 6.9 Hz, CH_2=CH–CH_2); IR (neat) 2982, 1955, 1667, 1449, 1435, 1291, 1209, 1166, 1070, 1031, 958, 835 cm^{-1}. Anal. Calcd. for $C_{13}H_{17}F_4NO$: C, 55.91; H, 6.14; N, 5.02. Found: C, 56.07; H, 6.13; N, 5.19.

*4.7. The preparation of N,N-diethyl-2-fluoro-3-(p-tolylthio)methyl-2-trifluoromethyl-3,4-hexadienamide (**2j**)*

To a solution of 5-(*p*-tolylthio)-3-pentyn-2-ol (420 mg, 1.4 mmol) and *N*,*N*-diisopropylethylamine (1.5 ml, 8.6 mmol) in dry chloroform (2.4 ml), was dropwise added a solution of PPDA (0.50 ml, 2.9 mmol) in dry chloroform (1.4 ml) over 11 min at room temperature. After the solution was stirred for 27 h, PPDA (0.24 ml, 1.4 mmol) in dry chloroform (1.4 ml) was added. The resulting solution was further stirred 13 h. The reaction was quenched with water (10 ml). The aqueous layer was separated and extracted with ether (3 × 10 ml). The combined organic layers were washed with 1N hydrochloric acid (3 × 20 ml) and 20 ml of brine (1 × 20 ml). The organic layer was dried over $MgSO_4$ and evaporated in vacuo to give an orange oil (1.09 g) that was chromatographed on silica gel [eluent: *n*-hexane–ethyl acetate (6:1)] to give *N*,*N*-diethyl-2-fluoro-3-(*p*-tolylthio)methyl-2-trifluoromethyl-3,4-decadienamide (**2j**) (518 mg: 92% yield). The diastereomeric ratio of **2j** could not be determined by ^{1}H NMR, because signals of the minor diastereomer was overlapped with the signals of the major isomer.

*4.7.1. N,N-Diethyl-2-fluoro-3-(p-tolylthio)methyl-2-trifluoromethyl-3,4-hexadienamide (**2j**)*

A colorless oil: bp 197 °C/5 mmHg (Kugelrohr distillation); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.12 (t, 3H, $J = 7.0$ Hz, CON(CH_2CH_3)), 1.15 (t, 3H, $J = 7.0$ Hz, CON(CH_2CH_3)), 1.52 (d, 3H, $J = 7.3$ Hz, CH_3CH=C), 2.32 (s, 3H, arom. CH_3), 2.97–3.14 (m, 2H, CON(CH_2CH_3) or CON(CH(H)CH_3)(CH(H)CH_3)), 3.49–3.69 (m, 2H, CON(CH_2CH_3) or CON(CH(H)CH_3)(CH(H)CH_3)), 3.66 (d, 3H, $J = 2.6$ Hz, CCH_2S), 5.39–5.48 (m, 1H, CH_3CH=C=CCF), 7.09 (d like, 2H, $J = 7.8$ Hz, arom. *H*), 7.25 (dd, 2H, $J = 8.4$, 2.0 Hz, arom. *H*); ^{19}F NMR (84.7 MHz, $CDCl_3$, external standard CF_3COOH) δ −86.82 (m, 1F, CF_3CF), 3.67 (d, 3F, $J = 6.1$ Hz, CF_3CF); IR (neat) 2978, 1967, 1660, 1493, 1448, 1435, 1290, 1209, 1165, 1130, 1084, 1030 cm^{-1}. Anal. Calcd. for $C_{19}H_{23}F_4NOS$: C, 58.60; H, 5.95; N, 3.60. Found: C, 58.90; H, 6.07; N, 3.47.

4.7.2. The preparation of 5-(p-tolythio)-3-pentyn-2-ol

The starting 5-(*p*-tolylthio)-3-pentyn-2-ol was prepared as follows; to a THF solution (20 ml) of propargyl(*p*-tolyl)-sulfide (974 mg, 6.0 mmol), a 1.58 M hexane solution

(4.6 ml) of *n*-butyllithium (7.2 mmol) was added at −78 °C. After the mixture was stirred for 12 min, acetaldehyde (500 μl) was added. The reaction was quenched with a saturated aqueous solution of NH_4Cl, and the resulting mixture was extracted with ether (4 × 10 ml). The combined organic layers were washed with brine, dried over $MgSO_4$ and evaporated in vacuo. The obtained crude mixture was chromatographed on silica gel column [eluent: *n*-hexane–ethyl acetate (4:1)] to give 5-(*p*-tolylthio)-3-pentyn-2-ol (805 mg: 65% yield).

4.7.2.1. 5-(p-Tolythio)-3-pentyn-2-ol. A pale yellow oil: bp 160 °C/4 mmHg (short path distillation); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.39 (d, 3H, $J = 6.5$ Hz, C*H*$_3$CHC≡C), 1.76 (diffused, 1H, CHO*H*), 2.34 (s, 3H, arom. C*H*$_3$), 3.59 (d, 2H, $J = 1.9$ Hz, CHC≡CC*H*$_2$S), 4.50 (q like, 1H, $J = 6.6$ Hz, CH$_3$C*H*C≡CCH$_2$), 7.14 (d, 2H, $J = 8.0$ Hz, arom *H*), 7.37 (dd, 2H, $J = 8.2$, 1.9 Hz, arom. *H*); IR (neat) 3356, 2979, 1493, 1448, 1406, 1369, 1232, 1155, 1078, 1003, 806 cm^{-1}. Anal. Calcd. for $C_{12}H_{14}OS$: C, 69.86; H, 6.84. Found: C, 69.63; H, 6.98.

*4.8. The preparation of N,N-diethyl-2-fluoro-3-(2-tetrahydropyranyloxy)methyl-2-trifluoromethyl-3,4-hexadienamide (**2k**)*

To a solution of 5-(2-tetrahydropyranyloxy)methyl-3-pentyn-2-ol (369 mg, 2.0 mmol) and *N*,*N*-diisopropylethylamine (2.1 ml, 12 mmol) in dry chloroform (2 ml), was dropwise added a solution of PPDA (0.71 ml, 4.0 mmol) in dry chloroform (2 ml) over 12 min at room temperature. After being stirred for 47 h, the reaction was quenched with a saturated aqueous solution of $NaHCO_3$ (10 ml). The aqueous layer was separated and extracted with ether (3 × 10 ml). The combined organic layers were washed with saturated aqueous solution of $NaHCO_3$ (2 × 10 ml), dried over $MgSO_4$–K_2CO_3 and evaporated in vacuo to give an orange oil (923 mg), that was chromatographed on silica gel [eluent: *n*-hexane–ethyl acetate (8:1)] to give *N*,*N*-diethyl-2-fluoro-3-(2-tetrahydropyranyloxy)methyl-2-trifluoromethyl-3,4-decadienamide (**2k**) (492 mg: 67% yield).

*4.8.1. N,N-Diethyl-2-fluoro-3-(2-tetrahydropyranyloxy)methyl-2-trifluoromethyl-3,4-hexadienamide (**2k**)*

A colorless oil: bp 144 °C/6 mmHg (short path distillation); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.13 (t, 3H, $J = 7.0$ Hz, CON(CH$_2$C*H*$_3$)), 1.17 (t, 1.5H, $J = 6.7$ Hz, CON(CH$_2$C*H*$_3$)), 1.19 (t, 1.5H, $J = 6.9$ Hz, CON-(CH$_2$C*H*$_3$)), 1.46–1.87 (m, 4H, OCH$_2$(C*H*$_2$)$_2$CH$_2$O), 1.73 (d, 3H, $J = 7.3$ Hz, C*H*$_3$CH=C), 3.06–3.23 (m, 2H, CON(C*H*$_2$CH$_3$) or CON(C*H*(H)CH$_3$)(C*H*(H)CH$_3$)), 3.47–3.90 (m, 4H, CON(C*H*$_2$CH$_3$) or CON(C*H*(H)CH$_3$)(C*H*-(H)CH$_3$) and CH$_2$C*H*$_2$OCH), 4.10–4.19 (m, 1H, C=CC*H*(H)O), 4.33–4.41 (m, 1H, C=CCH(*H*)O), 4.65–4.70 (m, 1H, CH$_2$C*H*O$_2$), 4.69 (t, 0.5H, $J = 3.3$ Hz, CH$_2$C*H*O$_2$), 5.53 (m, 1H, CH$_3$C*H*=C=CCF); IR (neat) 2943, 1973, 1666, 1454, 1385, 1292, 1209, 1165, 1120, 1038, 966, 835 cm^{-1}. Anal. Calcd. for $C_{17}H_{25}F_4NO_3 \cdot 0.2H_2O$: C, 55.04; H, 6.90; N, 3.78. Found: C, 54.99; H, 6.88; N, 3.38. LRMS (EI, 70 eV) 367 (M^+, 17.4%), 298 (100%), 283 (9.68%), 266 (78.6%), 214 (44.4%), 198 (22.2%), 100 (30.0%), 85 (60.4%), 72 (29.7%).

*4.9. The reaction of enantiomerically pure (S)-1-pentyn-3-ol ((S)-**1f**) with PPDA*

(*S*)-1-Pentyn-3-ol ((*S*)-**1f**) was prepared by an optical resolution of the half ester of phthalic acid of (*rac*)-1-pentyn-3-ol (**1f**) using brucine as a chiral base. The enantiomeric excess of (*S*)-**1f** was determined by ^{1}H NMR using a shift reagent Eu(hfc)$_3$, showing that (*S*)-**1f** was enantiomerically pure.

The thus-obtained (*S*)-**1f** was subjected to the reaction with 2 eq. of PPDA; To a solution of (*S*)-**1f** (252 mg, 3.0 mmol) and *N*,*N*-diisopropylethylamine (3.14 ml, 18 mmol) in dry chloroform (6 ml), was dropwise added a solution of PPDA (1.1 ml, 6.0 mmol) in dry chloroform (3 ml) over 8 min at room temperature. The resulting solution was stirred for 46 h at room temperature, and then quenched with water (10 ml). The aqueous layer was separated and extracted with chloroform (4 × 10 ml). The combined organic layers were washed with 1N hydrochloric acid (3 × 10 ml) and brine (2 × 10 ml), dried over $MgSO_4$ and evaporated in vacuo to give an orange oil (1.14 g). By ^{1}H NMR analysis, the yield of **2f** was determined to be 76%. The crude mixture was chromatographed on silica gel [eluent: *n*-hexane–ethyl acetate (6:1)] to give **2f*** (576 mg: 66% yield) that was further purified by Kugelrohr distillation. The diastereomeric ratio of **2f*** was 93:7 [by YMC Pack 60A-equipped HPLC; *n*-hexane–ethyl acetate (16:1)]. The two diastereomers **2f*** major and **2f*** minor were separated by preparative HPLC [YMC pack 60A: *n*-hexane–ethyl acetate (2:1)] followed by Kugelrohr distillation and a short-path distillation, respectively. The enantiomeric excess of each diastereomer was determined by ^{1}H NMR using shift reagent [Eu(hfc)$_3$] technique (see supplementary material).

*4.9.1. (S)-**1f***

A colorless oil: bp 112 °C/487 mmHg (Kugelrohr distillation). This oil was identified with racemic **1f** by ^{1}H NMR and IR. $[\alpha]_D^{25} = 0.39°$ ($c = 2.8$, $CHCl_3$).

*4.9.2. The major diastereomer of **2f***

A colorless oil: bp 88 °C/5 mmHg (Kugelrohr distillation). This oil was identified with racemic **2f** major by ^{1}H NMR and IR. $[\alpha]_D^{25} = 45.7°$ ($c = 0.42$, $CHCl_3$).

*4.9.3. The minor diastereomer of **2f***

A colorless oil: 80 °C/3 mmHg (short path distillation). This oil was identified with racemic **2f** minor by ^{1}H NMR and IR. $[\alpha]_D^{25} = 134°$ ($c = 0.40$, $CHCl_3$).

References

[1] H. Staudinger, L. Ruzicka, Helv. Chim. Acta 7 (1924) 177–201.

[2] (a) W.D. Celemer, I.A. Solomons, J. Am. Chem. Soc. 74 (1952) 1870–1871;
(b) W.D. Celemer, I.A. Solomons, J. Am. Chem. Soc. 74 (1952) 2245–2248;
(c) W.D. Celemer, I.A. Solomons, J. Am. Chem. Soc. 74 (1952) 3838–3842.

[3] M.J. McGrath, M.T. Fletcher, W.A. König, C.J. Moore, B.W. Cribb, P.G. Allsopp, W. Kitching, J. Org. Chem. 68 (2003) 3739–3748.

[4] D.F. Horler, J. Chem. Soc. C (1970) 859–862.

[5] (a) R. Filler, Y. Kobayashi (Eds.), Biomedicinal Aspects of Fluorine Chemistry, Kodansha, Elsevier, Tokyo, 1982;
(b) J.T. Welch, S. Eswarakrishnan, Fluorine in Bioorganic Chemistry, Wiley, New York, 1991;
(c) G. Resnati, Tetrahedron 49 (1993) 9385–9445.

[6] (a) F. Tellier, M. Audouin, R. Sauvêtre, Tetrahedron Lett. 42 (2001) 2665–2667;
(b) Z. Wang, G.B. Hammond, J. Org. Chem. 65 (2000) 6547–6552;
(c) T. Konno, M. Tanikawa, T. Ishihara, H. Yamanaka, Chem. Lett. (2000) 1360–1361;
(d) T. Konno, T. Kitazume, Chem. Commun. (1996) 2227–2228;
(e) D.J. Burton, G.A. Hatgraves, J. Hsu, Tetrahedron Lett. 31 (1990) 3699–3702;
(f) M.-H. Hung, Tetrahedron Lett. 31 (1990) 3703–3706;
(g) C.-M. Hu, F.-L. Qing, W.-Y. Huang, J. Org. Chem. 56 (1991) 2801–2804;
(h) Y. Hanzawa, K. Kawagoe, A. Yamada, Y. Kobayashi, Tetrahedron Lett. 26 (1985) 219–222;
(i) G. Shi, Y. Xu, J. Fluorine Chem. 44 (1989) 161–166;
(j) P.D. Lander, in: S.R. Landor (Ed.), The Chemistry of the Allenes, vol. 1, Academic Press, New York, 1982, p. 75;
(k) W.R. Dolbier Jr., C.R. Burkholder, J. Org. Chem. 49 (1984) 2381–2386;
(l) W.R. Dolbier Jr., C.R. Burkholder, W.R. Wincester, J. Org. Chem. 49 (1984) 1518–1522;
(m) W.R. Dolbier Jr., C.A. Burkholder, C.A. Piedrahita, J. Fluorine Chem. 20 (1982) 637–647;
(n) P.W.L. Bosbury, R. Fields, R.N. Haszeldine, J. Chem. Soc., Perkin Trans. 1 (1978) 422–427;
(o) P.W.L. Bosbury, R. Fields, R.N. Haszeldine, D. Moran, J. Chem. Soc., Perkin Trans. 1 (1976) 1173–1177;
(p) W.H. Knoth, D.D. Coffman, J. Am. Chem. Soc. 82 (1960) 3873–3875.

[7] J.A. Cooper, C.M. Olivares, G. Sandford, J. Org. Chem. 66 (2001) 4887–4891.

[8] (a) H.F. Schuster, G.M. Coppola, Allenes in Organic Synthesis, Wiley, New York, 1984;
(b) Z. Wan, S.G. Nelson, J. Am. Chem. Soc. 122 (2000) 10470–10471;
(c) P.A. Wender, L. Zhang, Org. Lett. 2 (2000) 2323–2326.

[9] (a) A.G. Myers, B. Zheng, J. Am. Chem. Soc. 118 (1996) 4492–4493;
(b) J.S. Cowie, P.D. Landor, S.R. Landor, J. Chem. Soc., Perkin Trans 1 (1973) 720–724;
(c) C.J. Elsevier, P. Vermeer, J. Org. Chem. 54 (1989) 3726–3730.

[10] T. Konoike, Y. Araki, Tetrahedron Lett. 33 (1992) 5093–5096.

[11] (a) G.A. Moniz, J.L. Wood, J. Am. Chem. Soc. 123 (2001) 5095–5097;
(b) J.A. Marshall, E.D. Robinson, A. Zapata, J. Org. Chem. 54 (1989) 5854–5855.

[12] (a) K.A. Parker, J.J. Petraitis, R.W. Koseley Jr., S. Buchwald, J. Org. Chem. 47 (1982) 389–398;
(b) K.A. Parker, R.W. Kosley Jr., Tetrahedron Lett. (1975) 3039–3040;
(c) K.A. Parker, R.W. Kosley Jr., Tetrahedron Lett. (1976) 341–344;
(d) G. Saucy, R. Marbet, Helv. Chim. Acta 50 (1967) 1158–1167;
(e) D.K. Black, Z.T. Fomum, P.D. Landor, S.R. Landor, J. Chem. Soc., Perkin Trans. 1 (1973) 1349–1352.

[13] K. Ogu, M. Akazome, K. Ogura, Tetraherdron Lett. 39 (1998) 305–308.

[14] Y. Umezawa, S. Tsuboyama, J. Uzawa, M. Nishio, Tetrahedron 55 (1999) 10047–10056.

[15] (a) D. Hoppe, C. Gonschorrek, D. Schmidt, E. Egert, Tetrahedron 43 (1987) 2457–2466;
(b) U. Kazmair, Libigs Ann./Recueil (1997) 285–295.

[16] K. Ogura, K. Ogu, T. Ayabe, J. Sonehara, M. Akazome, Tetrahedron Lett. 38 (1997) 5173–5176.

[17] (a) F.C. McGrew, R. Adams, J. Am. Chem. Soc. 59 (1937) 1497–1500;
(b) C.S.L. Baker, P.D. Landor, A.N. Patel, J. Chem. Soc. (1965) 4348–4354.

[18] H.L. Goering, G.S.K. Eikenberry, G.S. Koermer, C. Lattimer, J. Am. Chem. Soc. 96 (1974) 1493–1501.

[19] A. Takaoka, H. Iwakiri, N. Ishihara, Bull. Chem. Soc. Jpn. 52 (1979) 3377–3380.

[20] A. Altomare, G.L. Cascarano, C. Giacovazzo, A. Guagliardi, M.C. Burla, G. Polidori, M. Camalli, J. Appl. Cryst. 27 (1994) 435.