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Palladium-catalyzed reaction of functionalized β-trifluoromethyl vinyl bromides with terminal alkynes and alkenes

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Abstract

Palladium-catalyzed cross-coupling reaction of β-amino and β-ethoxy-β-trifluoromethyl vinyl bromides with terminal alkynes and terminal olefins has been achieved to afford new CF_3-substituted 1,3-enynes and 1,3-dienes, which can undergo carbolithiation.
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1. Introduction

α-CF_3-substituted enol ethers and enamines are readily available through the Wittig olefination of trifluoroacetic esters [1] and amides [2]. They have been shown to be suitable versatile building blocks in particular for the preparation of tetrasubstituted functionalized alkenes, either through a carbolithiation–elimination–metallation cascade [3,4] or by Suzuki cross-coupling reactions [5,6] of the corresponding vinyl bromides **1**–**4**. In this connection, we have investigated other palladium catalyzed cross-coupling reactions between vinyl bromides and terminal alkenes and alkynes. In this paper, we report results about the use of β-ethoxy and β-amino-trifluoromethyl vinyl bromides in Heck and Sonogashira type reactions in order to obtain various CF_3-substituted 1,3-enynes and 1,3-dienes (Scheme 1).

2. Results and discussion

2.1. The Heck reaction

First, we investigated the Heck reaction with the β-trifluoromethyl vinyl bromides **1** (*Z*/*E*, 70:30) and **2** (*Z*/*E*, 90:10) and styrene (**5a**) in the presence of $Pd(PPh_3)_4$ at reflux in triethylamine, under conditions described with other vinyl bromides in the literature [7,8]. The cross-coupling products **6a** and **7a** were obtained in moderate yields (68 and 58%, respectively) as a mixture of 70:30 and 90:10 *Z*/*E* isomers, respectively. In order to improve yields, the reaction was performed in DMF at high temperature (135°C) under Jeffery's conditions ([Pd], K_2CO_3, Bu_4NBr) [9]. No product was formed: at this temperature **1** decomposed and **2** did not react. Nevertheless, under the same conditions, but without any phase transfer agent, reaction could occur between the β-ethoxy vinyl bromide **2** and styrene, and yield of **7a** could be improved (80%). However, this reaction was limited to styrene. With methylacrylate, no reaction occurred at 135°C. Reflux of DMF (153°C) was required to afford **7b** in only low yield (34%). At this high temperature, the vinyl bromide **2** decomposed within 0.5 h. No cross-coupling product could be obtained with methylvinylketone (results are presented in Table 1).

Compounds **6a** [6] and **7a** [5] were already described. For compound **7c**, the stereochemistry was unambiguously determined by ^1H and ^{19}F NMR experiments. For the minor isomer of **7c**, the irradiation of CF_3 entailed a NOE (9%) on the signal of a vinylic proton indicating their spatial proximity and hence a *Z* configuration. As expected, the Heck reaction is stereospecific [7,8].

2.2. The Sonogashira reaction

Next we envisaged to prepare enynes by palladium catalyzed cross-coupling reaction between vinyl bromides and terminal alkynes, using the classical Sonogashira reaction conditions ([Pd] cat., CuI cat. at reflux of Et_3N) [10,11]. Under these conditions, in the presence of $Pd(OAc)_2/2PPh_3$

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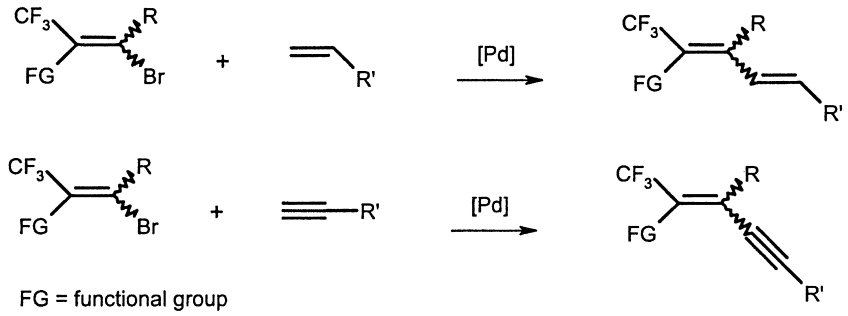


Scheme 1.

and CuI as catalysts, enynes could not be obtained even at reflux of Et_3N.

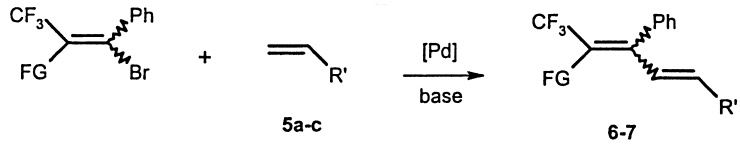
Surprisingly, when the reaction was performed without CuI at reflux of Et_3N, the β-trifluoromethyl-β-amino vinyl bromide **1** reacted with phenylacetylene (**8a**) to afford the enyne **9a** in moderate yield as a 70:30 mixture of *Z*/*E* isomers (Table 2, entry 1, 60%). By the use of $Pd(PPh_3)_4$ instead of $Pd(OAc)_2/2PPh_3$, the enyne **9a** could be obtained in quantitative yield (Entry 2, 95%). The reaction was then investigated under these conditions between vinyl bromides **1**–**4** and terminal alkynes **8a**–**d** (R′ = Ph, *n*-Bu, TMS, $C(Me)_2OH$) (results are reported in Table 2). The reaction was efficient in all cases, and enynes **9a**–**c**, **10a**–**c**, **11c** and **12c** could be obtained in excellent yields. With alkyne **8d**, yield in enyne was lower, starting from β-amino or β-ethoxy vinyl bromide **1** and **2**.

As expected, the reaction is stereospecific. The stereochemistry of **9c** was unambiguously determined by ^{1}H NMR experiments. For the minor isomer of **9c**, a NOESY analysis showed a correlation between CH_2N and the ortho proton of the phenyl group, indicating their spatial proximity. So, the major isomer of **9c** has a *Z* configuration. Stereochemistry of **9a**, **b** and **d** has been determined by comparison of their ^{19}F NMR chemical shifts with those of **9c** (Section 4). The stereochemistry of **10c** was unambiguously determined by ^{1}H NMR experiments. For the major isomer of **10c**, a NOESY analysis showed a correlation between CH_2O and Me_3Si protons. So the major isomer has a *Z* configuration. Stereochemistry of **10a**, **b** and **d** and **12c** has been determined by comparison of their ^{19}F NMR chemical shifts with those of **10c** (Section 4).

We previously described that α-CF_3 β-phenyl enol ethers could undergo an addition/elimination reaction with organolithium reagents, resulting in a stereoselective replacement of the ethoxy group by the organic part of the lithium reagent [3,4]. We investigated this reaction with β-disubstituted enol ethers **10a**–**c** obtained by Sonogashira type cross-coupling reaction. While **10b** and **c** readily reacted with *n*-BuLi, leading to **13b** and **c**, **10a** was unreactive even after 3 h. However, unlike reactions performed with β-monosubstituted enol ethers, the reaction is not stereoselective: starting from *Z*/*E* 90:10, a 70:30 mixture of *E*/*Z* isomers was obtained for products **13b** and **c** (Table 3).

The stereochemistry of **13b** has been determined by ^{1}H and ^{19}F NMR experiments. For the major isomer of **13b**, the irradiation of CF_3 entailed a NOE (4%) on the signal of aromatic protons, indicating their spatial proximity. So, the major isomer has an *E* configuration. The stereochemistry of

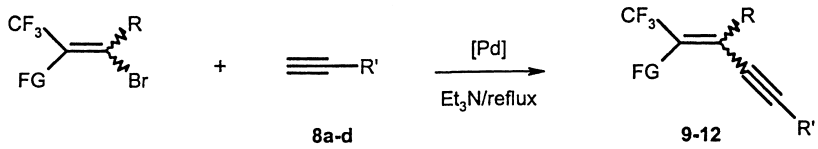
Table 1
Palladium-catalyzed reaction of β-trifluoromethyl-β-amino and β-ethoxy vinyl bromides with alkenes[a]



1 FG = morpholine *Z*/*E* 70:30
2 FG = EtO *Z*/*E* 90:10

Substrate	**5** (R′)	[Pd]	Solvent	Temperature (°C)	Reaction time (h)	Product **6**–**7**	Yield (%)
1	**a**: Ph	$Pd(PPh_3)_4$	Et_3N	88	24	**6a**	68
1	**b**: CO_2Me	$Pd(PPh_3)_4$	Et_3N	88	25	**6b**	0
2	**a**: Ph	$Pd(PPh_3)_4$	Et_3N	88	25	**7a**	58
2	**a**: Ph	$Pd(PPh_3)_4$	DMF	135	3	**7a**	80
2	**b**: CO_2Me	$Pd(PPh_3)_4$	DMF	153	0.5	**7b**	34
2	**c**: COMe	$Pd(PPh_3)_4$	DMF	153	0.5	**7c**	0

Table 2
Palladium-catalyzed reaction of β-trifluoromethylated-β-amino and β-ethoxy vinyl bromides with alkynes



8a-d **9-12**

1 : FG = morpholine, R = Ph *Z*/*E* 70/30

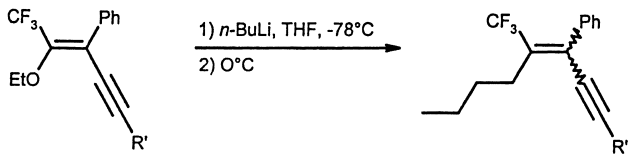
2 : FG = OEt, R = Ph *Z*/*E* 90/10

3 : FG = morpholine, R = $(CH_2)_2Ph$ *Z*/*E* 90/10

4 : FG = OEt, R = $(CH_2)_2Ph$ *Z*/*E* 90/10

Entry	Substrate **1–4**	**8** (R′)	[Pd]	Reaction time (h)	Product **9–12**	Yield (%)
1	**1**	**a**: Ph	$Pd(OAc)_2/2PPh_3$	0.5	**9a**	60
2	**1**	**a**: Ph	$Pd(PPh_3)_4$	0.5	**9a**	95
3	**1**	**b**: $(CH_2)_3Me$	$Pd(PPh_3)_4$	2	**9b**	87
4	**1**	**c**: $SiMe_3$	$Pd(PPh_3)_4$	0.5	**9c**	92
5	**1**	**d**: $C(Me)_2OH$	$Pd(PPh_3)_4$	1	**9d**	60
6	**2**	**a**: Ph	$Pd(PPh_3)_4$	3	**10a**	95
7	**2**	**b**: $(CH_2)_3Me$	$Pd(PPh_3)_4$	3	**10b**	87
8	**2**	**c**: $SiMe_3$	$Pd(PPh_3)_4$	1	**10c**	86
9	**2**	**d**: $C(Me)_2OH$	$Pd(PPh_3)_4$	1.5	**10d**	50
10	**3**	**c**: $SiMe_3$	$Pd(PPh_3)_4$	5	**11c**	74
11	**4**	**c**: $SiMe_3$	$Pd(PPh_3)_4$	6	**12c**	68

Table 3
Preparation of alkylenynes from ethoxyenynes



10a-c **13a-c**

Z/*E* 90:10 *E*/*Z* 70:30

Substrates	R′	Reaction time (h)	Product	Yield (%)
10a	Ph	3	**13a**	0
10b	$(CH_2)_3Me$	0.75	**13b**	70
10c	$SiMe_3$	0.75	**13c**	67

13c has been determined by comparison of ^{19}F NMR chemical shifts with those of **13b** (Section 4).

3. Conclusions

We have presented a preparation of trifluoromethyl dienes and enynes via the palladium-catalyzed cross-coupling reaction of β-trifluoromethyl-β-amino vinyl bromides and β-trifluoromethyl-β-ethoxy vinyl bromides with terminal alkenes and alkynes. This easy access of CF_3-substituted dienes and enynes is an attractive entry into this class of trifluoromethyl building blocks.

4. Experimental

^{19}F NMR, ^{13}C NMR, ^{1}H NMR spectra were recorded on a Bruker AC-200 MHz multinuclear spectrometer. Chemical shifts (δ) are given in ppm relative to $CFCl_3$ for ^{19}F NMR, and relative to TMS for ^{1}H NMR and ^{13}C NMR. Coupling constants are given in Hz. In all measurements $CDCl_3$ was used as a solvent. IR spectra were recorded on a Bruker Vector 22 spectrometer. GC analyses were performed using a SE 30 capillary column (12 m). All the alkynes used are commercially available. $Pd(PPh_3)_4$ [12], vinyl bromides **1–2** [6], and **3–4** [5], dienes **6a** [6] and **7a** [5] were already described. The petroleum ether used has a 40–65°C bp.

5. Preparation of dienes and enynes

5.1. General procedure for Heck cross-coupling (*6a* and *7a*)

To a solution of vinyl bromide **1** (100 mg, 0.30 mmol) or **2** (100 mg, 0.39 mmol) and $Pd(PPh_3)_4$ (5 mol%) in Et_3N, styrene was added (2 mol eq). The mixture was refluxed 24–25 h (the reaction was monitored by GC). After washing with an aqueous saturated NH_4Cl solution, the aqueous phase was extracted with Et_2O. The combined organic phases were dried ($MgSO_4$) and concentrated to give after chromatography on silica gel (petroleum ether/Et_2O, 95:5) pure dienes **6a** (73 mg, 68%) and **7a** (72 mg, 58%).

*5.1.1. (Z/E)-5-ethoxy-6,6,6-trifluoromethyl-4-phenyl-methylhexa-2,4-dienoate (**7b**)*

To a solution of vinyl bromide **2** (100 mg, 0.34 mmol), $Pd(PPh_3)_4$ (20 mg, 0.017 mmol) and K_2CO_3 (117 mg, 0.85 mmol) in DMF (6 ml), under argon atmosphere, methylacrylate (241 mg, 2.8 mmol) was added. The mixture maintained at reflux for 0.5 h (the reaction was monitored by GC). After washing with an aqueous saturated NH_4Cl solution, the aqueous phase was extracted with Et_2O (2×15 ml). The combined organic phases were washed with brine (2×20 ml), dried ($MgSO_4$) and concentrated to give after chromatography on silica gel (petroleum ether/EtOAc, 90:10), pure diene **7b** as a colorless oil (35 mg, 34%); IR υ (cm^{-1}) 1622, 1721; ^{19}F NMR δ: −61.5(*E*)/−61.6(*Z*) (90:10) (s, CF_3); ^1H NMR δ: 0.9(*Z*)/1.5(*E*) (t, $J = 7.0$ Hz, 3H), 3.6(*Z*)/4.1(*E*) (q, $J = 7.0$ Hz, 2H), 3.7 (s, 3H), 5.4 (*E*)/5.6 (*Z*) (d, $J = 16$ Hz, 1H), 7.0–7.5 (m, 5H), 8.0 (d, $J = 16$Hz, 1H); ^{13}C NMR δ: 15.0(*Z*)/15.2(*E*), 51.7, 70.6(*Z*)/71.7(*E*), 121.0 (q, $^1J_{C-F} = 278$ Hz, CF_3), 124.8(*Z*)/125.2(*E*), 128.2, 128.3, 129.3 (q, $^5J_{C-F} = 1.4$ Hz), 131.9 (q, $^3J_{C-F} = 3.1$ Hz, CF_3–C=*C*), 132.7(*E*)/133.9(*Z*), 139.1(*Z*) (q, $^4J_{C-F} = 3.1$ Hz)/140.3 (*E*), 144.8 (q, $^2J_{C-F} = 32$ Hz, CF_3–*C*), 166.6(*Z*)/166.8(*E*). Anal. Calcd. for $C_{15}H_{15}F_3O_3$ (300.28): C, 60.00; H, 5.03. Found: C, 60.17; H, 5.35%.

*5.2. (Z/E)-5,5,5-trifluoromethyl-4-morpholino-1,3-diphenylpent-3-en-1-yne (**9a**): typical procedure*

To a solution of vinyl bromide **1** (100 mg, 0.3 mmol) and $Pd(PPh_3)_4$ (17 mg, 0.015 mmol) in Et_3N (6 ml) under argon atmosphere, phenylacetylene (61 mg, 0.6 mmol) was added. The mixture was refluxed for 0.5 h. After washing with saturated NH_4Cl, the organic phase was extracted with ether (2×15 ml). The combined organic phases were dried ($MgSO_4$) and concentrated to give after chromatography on silica gel (petroleum ether/Et_2O, 95:5), pure enyne **9a** as a brown oil (101 mg, 95%); IR υ (cm^{-1}): 1598, 2197; ^{19}F NMR δ: −59.1(*Z*)/−61.6(*E*) (70:30) (s, CF_3); ^1H NMR δ: 2.7(*E*)/3.4(*Z*) (t, $J = 4.5$ Hz, 4H), 3.5(*E*)/3.8(*Z*) (t, $J = 4.5$ Hz, 4H), 7.1–7.5 (m, 10H); ^{13}C NMR δ: 51.2(*Z*)/51.9(*E*), 67.0(*E*)/67.7(*Z*), 88.4, 103.2, 122.8 (q, $^1J_{C-F} = 284$ Hz, CF_3), 128.1, 128.4, 128.5, 128.6 (q, $^5J_{C-F} = 2.4$ Hz), 129.0, 134.1, 136.6, 137.8, 141.2 (q, $^2J_{C-F} = 30$ Hz, CF_3–*C*).

*5.2.1. (Z/E)-1,1,1-trifluoromethyl-2-morpholino-3-phenylnon-2-en-1-yne (**9b**)*

Starting from **1**, afforded **9b** (88 mg, 87%), brown oil; IR υ (cm^{-1}): 1587, 2215; ^{19}F NMR δ: −59.1(*Z*)/−61.6(*E*) (70:30) (s, CF_3); ^1H NMR δ: 0.9 (t, $J = 7.0$ Hz, 3H), 1.3–1.6 (m, 6H), 2.4 (t, $J = 6.8$ Hz, 2H), 2.7(*Z*)/3.3(*E*) (t, $J = 4.6$ Hz, 4H), 3.5(*Z*)/3.7(*E*) (t, $J = 4.6$ Hz, 4H), 7.1–7.4 (m, 5H); ^{13}C NMR δ: 13.5(*Z*)/13.9(*E*), 19.5(*Z*)/19.6(*E*), 21.8 (*Z*)/22.1(*E*), 30.5(*Z*)/30.9(*E*), 50.8(*E*)/51.7(*Z*), 66.9(*Z*)/67.6(*E*), 77.9(*Z*)/79.6(*E*), 99.7(*Z*)/102.7(*E*), 119.6 (q, $^3J_{C-F} = 2.3$ Hz, CF_3–C=*C*), 123.0 (q, $^1J_{C-F} = 280$ Hz, CF_3), 127.9, 128.2, 128.8, 137.3(*E*)/138.4(*Z*), 140.7 (q, $^2J_{C-F} = 29$ Hz, CF_3–*C*).

*5.2.2. (Z/E)-5,5,5-trifluoromethyl-1-trimethylsilyl-4-morpholino-3-phenylpent-3-en-1-yne (**9c**)*

Starting from **1** (970 mg, 2.9 mmol), afforded **9c** (941 mg, 92%), brown oil; IR υ (cm^{-1}): 1583, 2135; ^{19}F NMR δ: −58.9(*Z*)/−61.3(*E*) (70:30) (s, CF_3); ^1H NMR δ: 0.19(*E*)/0.21(*Z*) (s, 9H), 2.7(*E*)/3.3(*Z*) (t, $J = 4.5$ Hz, 4H), 3.6(*E*)/3.8(*Z*) (t, $J = 4.5$ Hz, 4H), 7.2–7.4 (m, 5H); ^{13}C NMR δ: −0.5(*Z*)/−0.6(*E*), 50.7(*Z*)/51.6(*E*), 66.5(*E*)/67.2(*Z*), 101.9(*E*)/103.3(*Z*), 102.8(*E*) (q, $^5J_{C-F} = 1.9$ Hz)/105.7(*Z*), 121.4 (q, $^3J_{C-F} = 2.9$ Hz, CF_3–C=*C*), 122.5 (q, $^1J_{C-F} = 278$ Hz, CF_3), 127.7, 128.1, 128.3 (q, $^5J_{C-F} = 1.9$ Hz), 136.2(*Z*)/137.4(*E*), 142.2 (q, $^2J_{C-F} = 29$ Hz, CF_3–*C*).

*5.2.3. (Z/E)-6,6,6-trifluoromethyl-1,1-dimethyl-5-morpholino-4-phenylhex-4-en-2-yn-1-ol (**9d**)*

Starting from **1** (300 mg, 0.89 mmol), afforded **9d** (182 mg, 60%), brown oil; IR υ (cm^{-1}): 1677, 3391; ^{19}F NMR δ: −58.9(*Z*)/−61.5(*E*) (70:30) (s, CF_3); ^1H NMR δ: 1.5(*Z*)/1.6(*E*) (s, 6H), 2.6(*E*)/3.2(*Z*) (t, $J = 4.6$ Hz, 4H), 3.5(*E*)/3.8(*Z*) (t, $J = 4.6$ Hz, 4H), 7.2–7.4 (m, 5H, C_6H_5), OH n.o.; ^{13}C NMR δ: 31.0(*E*)/31.2(*Z*), 50.6(*Z*)/51.7(*E*), 65.4(*Z*)/65.6(*E*), 66.8(*E*)/67.5(*Z*), 79.5(*E*)/80.6(*Z*), 102.0(*E*) (q, $^5J_{C-F} = 1.9$ Hz)/105.5(*Z*), 122.6(*Z*)/122.8(*E*) (q, $^1J_{C-F} = 279$ Hz, CF_3), 123.0 (q, $^3J_{C-F} = 2.7$ Hz, CF_3–C=*C*), 128.0, 128.4 (q, $^5J_{C-F} = 1.8$ Hz), 128.9, 136.6(*Z*)/137.7(*E*), 141.4(*Z*)/141.5(*E*) (q, $^2J_{C-F} = 29$ Hz, CF_3–*C*). Anal. Calcd. for $C_{18}H_{20}F_3NO_2$ (339.36): C, 63.71; H, 5.94; N, 4.13. Found: C, 64.05; H, 6.01; N, 3.92%.

*5.2.4. (Z/E)-4-ethoxy-5,5,5-trifluoromethyl-1,3-diphenylpent-3-en-1-yne (**10a**)*

Starting from **2** (103 mg, 0.34 mmol), afforded **10a** (105 mg, 95%), brown oil; IR υ (cm^{-1}): 1613, 2201; ^{19}F NMR δ: −62.9(*Z*)/−65.0(*E*) (90:10) (s, CF_3); ^1H NMR δ: 1.2(*E*)/1.5(*Z*) (t, $J = 7.0$ Hz, 3H), 3.5(*E*)/4.4(*Z*) (q, $J = 7.0$ Hz, 2H), 7.3–7.5 (m, 10H); ^{13}C NMR δ: 15.7, 71.0, 86.0, 99.6, 117.8 (q, $^3J_{C-F} = 3.0$ Hz, CF_3–C=*C*), 121.2 (q, $^1J_{C-F} = 277$ Hz, CF_3), 128.2, 128.4, 128.7 (q, $^5J_{C-F} = 1.9$ Hz), 128.9, 131.5, 134.7, 147.8 (q, $^2J_{C-F} = 33$ Hz, CF_3–*C*).

*5.2.5. (Z/E)-2-ethoxy-1,1,1-trifluoromethyl-3-phenylnon-2-en-4-yne (**10b**)*

Starting from **2** (100 mg, 0.34 mmol), afforded **10b** (88 mg, 87%), brown oil; ^{19}F NMR δ: −62.8(*Z*)/−65.0(*E*) (90:10) (s, CF_3); ^1H NMR δ: 0.9 (t, $J = 7.0$ Hz, 3H), 1.1(*E*)/1.4(*Z*) (t, $J = 7.0$ Hz, 3H), 1.2–1.3 (m, 4H), 2.4 (t, $J = 6.8$ Hz, 2H), 3.5(*E*)/4.2(*Z*) (t, $J = 7.0$ Hz, 2H), 7.2–7.4 (m, 5H); ^{13}C NMR δ: 13.5, 15.5, 19.6, 22.0, 30.6, 70.5, 77.4, 101.9, 118.7 (q, $^3J_{C-F} = 2.7$ Hz, CF_3–C=*C*), 121.3 (q, $^1J_{C-F} = 278$ Hz, CF_3), 128.1, 128.2, 129.0 (q, $^5J_{C-F} = 1.9$ Hz), 135.3.

*5.2.6. (Z/E)-4-ethoxy-5,5,5-trifluoromethyl-1-trimethylsilyl-3-phenylpent-3-en-1-yne (**10c**)*

Starting from **2** (500 mg, 1.7 mmol), afforded **10c** (454 mg, 86%), brown oil; IR υ (cm^{-1}): 1611, 2144; ^{19}F NMR δ: −63.2(*Z*)/−65.2(*E*) (90:10) (s, CF_3); ^1H NMR δ: 0.20(*Z*)/0.21(*E*) (s, 9H), 1.1(*E*)/1.4(*Z*) (t, $J = 7.0$ Hz, 3H), 3.7(*E*)/4.3(*Z*) (q, $J = 7.0$ Hz, 2H), 7.2–7.4 (m, 5H); ^{13}C NMR δ: −0.5(*E*)/−0.4(*Z*), 15.0(*E*)/15.4(*Z*), 70.3(*E*)/70.6(*Z*), 99.2(*E*)/100.9(*Z*), 104.4(*E*)/105.6(*Z*), 117.6 (q, $^3J_{C-F} = 3.0$ Hz, CF_3–C=*C*), 121.1 (q, $^1J_{C-F} = 277$ Hz, CF_3), 128.1, 128.3, 128.7 (q, $^5J_{C-F} = 1.9$ Hz), 134.3(*Z*)/134.5(*E*), 149.1 (q, $^2J_{C-F} = 33$ Hz, CF_3–*C*).

*5.2.7. (Z/E)-5-ethoxy-6,6,6-trifluoromethyl-1,1-dimethyl-4-phenylhex-4-en-2-yn-1-ol (**10d**)*

Starting from **2** (100 mg, 0.33 mmol), afforded **10d** (50 mg, 50%), brown oil; IR υ (cm^{-1}): 1617, 3357; ^{19}F NMR δ: −63.0 (*Z*)/−65.2(*E*) (90:10) (s, CF_3); ^1H NMR δ: 1.0(*E*)/1.3(*Z*) (t, $J = 7.0$ Hz, 3H), 1.4 (s, 6H), 1.6 (br, 1H, OH), 3.6(*E*)/4.2(*Z*) (q, $J = 7.0$ Hz, 2H), 7.2–7.4 (m, 5H, C_6H_5); ^{13}C NMR δ: 15.5, 31.1, 65.7, 70.7, 78.8, 104.1, 121.0 (q, $^1J_{C-F} = 277$ Hz, CF_3), 128.1, 128.4, 128.6, 134.4; 148.5 (q, $^2J_{C-F} = 31$ Hz, CF_3–*C*). Anal. Calcd. for $C_{16}H_{17}F_3O_2$ (298.30): C, 64.42; H, 5.74. Found: C, 64.77; H, 5.93%.

*5.2.8. (Z/E)-5,5,5-trifluoromethyl-1-trimethylsilyl-4-morpholino-3-(2-phenylethyl)-pent-3-en-1-yne (**11c**)*

Starting from **3** (1 g, 2.7 mmol), afforded **11c** (775 mg, 74%), brown oil; IR υ (cm^{-1}): 1603, 2140; ^{19}F NMR δ: −59.1(*Z*)/−59.9(*E*) (10:90) (s, CF_3); ^1H NMR δ: 0.2 (s, 9H), 2.5 (m, 4H), 3.1 (t, $J = 4.6$ Hz, 2H), 3.7 (t, $J = 4.6$ Hz, 2H), 7.1–7.5 (m, 5H); ^{13}C NMR δ: −0.3, 34.0, 34.8, 50.6, 67.3, 100.4, 106.1, 123.0 (q, $^1J_{C-F} = 286$ Hz, CF_3), 126.1, 126.9 (q, $^3J_{C-F} = 3.0$ Hz, CF_3–C=*C*), 128.3, 128.7 141.0, 141.8 (q, $^2J_{C-F} = 28$ Hz, CF_3–*C*).

*5.2.9. (Z/E)-4-ethoxy-5,5,5-trifluoromethyl-1-trimethylsilyl-3-(2-phenylethyl)-pent-3-en-1-yne (**12c**)*

Starting from **4** (800 mg, 2.5 mmol), afforded **12c** (574 mg, 68%), brown oil; IR υ (cm^{-1}): 1624, 2146; ^{19}F NMR δ: −63.2(*Z*)/−65.3(E) (90:10) (s, CF_3); ^1H NMR δ: 0.2 (s, 9H), 2.5 (m, 2H), 1.3 (t, $J = 7.0$ Hz, 3H), 2.9 (m, 2H), 4.0 (q, $J = 7.0$ Hz, 2H), 7.0–7.4 (m, 5H); ^{13}C NMR δ: −0.2, 15.4, 32.0, 34.9, 70.4, 94.3, 100.7, 117.4 (q, $^3J_{C-F} = 3.0$ Hz, CF_3–C=*C*), 121.5 (q, $^1J_{C-F} = 275$ Hz, CF_3), 126.1, 128.3, 128.4, 140.7, 148.4 (q, $^2J_{C-F} = 34$ Hz, CF_3–*C*).

*5.3. Preparation of (Z/E)-2-butyl-1,1,1-trifluoromethyl-3-phenylnon-2-en-4-yne (**13b**): typical procedure*

To a solution of ethoxyenyne **10b** (70 mg, 0.24 mmol) in THF (4 ml) under argon atmosphere, a solution of *n*-BuLi (0.26 mmol, 1.6 M in hexane) was added at −78°C. The solution was stirred for 15 min at this temperature and then was allowed to warm at 0°C for a period of 30 min. The solution was then poured into an aqueous saturated NH_4Cl solution, the layers were separated and the aqueous phase was extracted with Et_2O (2 × 15 ml). The combined organic phases were dried ($MgSO_4$) and solvents evaporated to afford after chromatography on silica gel (petroleum ether/Et_2O, 95:5), enyne **13b** as a yellow oil (52 mg, 70%); IR υ (cm^{-1}): 1614, 2216; ^{19}F NMR δ: 57.2(*E*)/−61.1(Z) (70:30) (s, CF_3); ^1H NMR δ: 0.7 (t, $J = 7.2$ Hz, 3H), 0.8–1.1 (m, 5H), 1.2–1.7 (m, 6H), 2.2(*Z*)/2.6(*E*) (t, $J = 7.2$ Hz, 2H), 2.4 (t, $J = 6.8$ Hz, 2H), 7.2–7.4 (m, 5H); ^{13}C NMR δ: 13.5, 13.8, 19.4, 21.9, 22.7, 30.5, 30.8, 32.0 (q, $^3J_{C-F} = 2.0$ Hz), 79.8, 95.5, 124.3 (q, $^1J_{C-F} = 275$ Hz, CF_3), 127.7, 127.8, 127.9 (q, $^5J_{C-F} = 1.9$ Hz), 134.8, 138.5 (q, $^2J_{C-F} = 26$ Hz, CF_3–*C*). Anal. Calcd. for $C_{19}H_{23}F_3$ (308.39): C, 74.00; H, 7.52. Found: C, 74.25; H, 7.50%.

*5.4. 4-Butyl-5,5,5-trifluoromethyl-1,1,1-trimethylsilyl-3-phenylpent-3-en-1-yne (**13c**)*

Starting from **10c** (100 mg, 0.32 mmol), afforded **13c** (70 mg, 67%), yellow oil; IR υ (cm^{-1}): 1598, 2143; ^{19}F NMR δ: 57.5(*E*)/−61.2(*Z*) (70:30) (s, CF_3); ^1H NMR δ: 0.1(*Z*)/0.2(*E*) (s, 9H), 0.7(*Z*)/1.0(*E*) (t, $J = 7.0$ Hz, 3H), 1.5 (m, 2H), 1.7 (m, 2H), 2.2(*Z*)/2.6(*E*) (t, $J = 7.6$ Hz, 2H), 7.2–7.4 (m, 5H); ^{13}C NMR δ: −0.5(*E*)/−0.3(*Z*), 13.5(*E*)/13.8(*Z*), 22.5(*E*)/22.8(*Z*), 30.7, 31.3 (q, $^3J_{C-F} = 2.0$ Hz), 94.2, 103.0, 124.1 (q, $^1J_{C-F} = 275$ Hz, CF_3), 127.9, 128.1, 128.4, 137.1, 137.6 (q, $^2J_{C-F} = 26$ Hz, CF_3–*C*). Anal. Calcd. for $C_{18}H_{23}F_3Si$ (324.46): C, 66.63; H, 7.14. Found: C, 66.95; H, 7.20%.

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