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Carbonyl-yne reactions of 3,3,3-trifluoropyruvates

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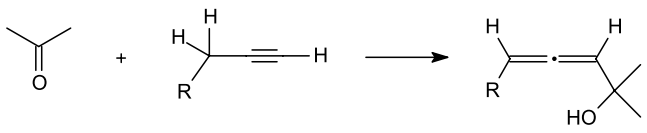
Abstract—An efficient synthesis of trifluoromethyl-containing 2,3-allenols via carbonyl-yne reaction of 3,3,3-trifluoropyruvates with acetylenes is described. In the presence of $MgBr_2{\cdot}Et_2O$ the reaction of methyl trifluoropyruvate with hex-1-yne proceeds diastereoselectively. Trifluoromethyl-substituted 2,3-allenols can be stereoselectively transformed into trifluoromethyl-substituted 2,5-dihydrofurans on treatment with $AgNO_3$.

1. Introduction

The reaction of activated carbonyl compounds and alkenes with allylic hydrogen atoms, represents an important carbon–carbon bond forming process.[1] Especially, asymmetric carbonyl-ene reactions catalyzed by chiral Lewis acids have received considerable attention.[2] Surprisingly, reports about the acetylenic variant of this reaction are rare (Scheme 1).

Strong enophiles (super-enophiles[1d]) like polyfluoroketones,[3] indane-1,2,3-trione,[4] alloxan,[5] and 1,3-dimethylalloxan[5] react with propyne and its homologues to give 2,3-allenols, which are of high synthetic value.[6] For example, 2,3-allenols serve as precursors for the synthesis of 2,5-dihydrofurans,[7] which are important building blocks in natural product synthesis. Herein we report on the reaction of 3,3,3-trifluoropyruvates with acetylenes having propargyl hydrogen atoms.



Scheme 1.

2. Results and discussion

3,3,3-Trifluoropyruvates are capable for carbonyl-ene reactions.[8a,b] Ketone **1a** reacts with olefins having allylic hydrogen atoms—depending on the structure of the olefins—in a temperature range from −20 to 150°C—to give α-hydroxy-α-trifluoromethyl-α-allylacetic acids. Carbonyl-ene reactions of methyl trifluoropyruvate **1a** can be promoted by Lewis acids like $SnCl_4$.[8a]

We found that heating of **1a** with propyne or hex-1-yne in a sealed tube at 80°C for 24 h in a clean reaction gives products **2** and **3** in good yields, respectively (Scheme 2).

According to ^{19}F NMR and GCMS analysis, compounds **2** and **3** are the only reaction products formed. In the case of hex-1-yne, yne reaction with **1a** gives product **3** as a 1:1 mixture of diastereomers. A more complex reaction pathway was observed in the case of the reaction of ethyl trifluoropyruvate **1b** with methyl propargyl ether (Scheme 3). On heating the components up to 70°C for 2 days, we isolated 2,5-dihydrofuran **5** as a 3:2 mixture of *trans*-/*cis*-isomers in 65% yield. The isomers were separated by column chromatography to give the pure main isomer in 31% yield. NOE experiments confirmed a *cis* relationship between the CF_3 group placed at C-2 and the C(5)–H, as shown in formula **5a**. Noteworthy, methyl trifluoropyruvate gave an unseparable mixture of 2,5-dihydrofurans.

Apparently, the electron-donating effect of the methoxy group along with the high acidity of the hydroxy group together with the elevated temperatures cause an uncatalyzed intramolecular cyclization of initially formed allenylcarbinol **4**. The same mechanistic type was found in the reaction of hexafluoroacetone with methyl propargyl ether.[9]

In general, the thermal carbonyl-yne reaction of **1a**,**b** with acetylene derivatives give diastereomeric mixtures in a ratio close to 1:1. To achieve diastereoselectivity for this reaction, we tried to initiate this process at low temperatures using Lewis acids. Attempts to promote the yne reaction of

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† Dedicated to our deceased colleague Professor Dr Alexey F. Kolomiets.

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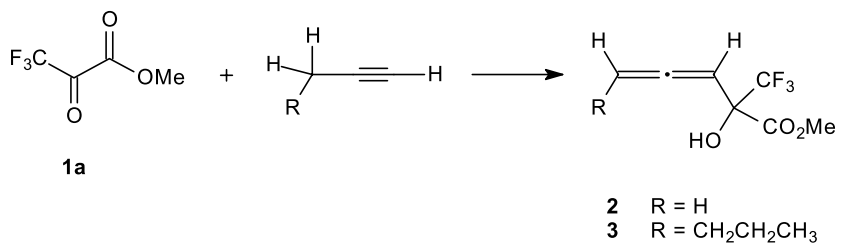
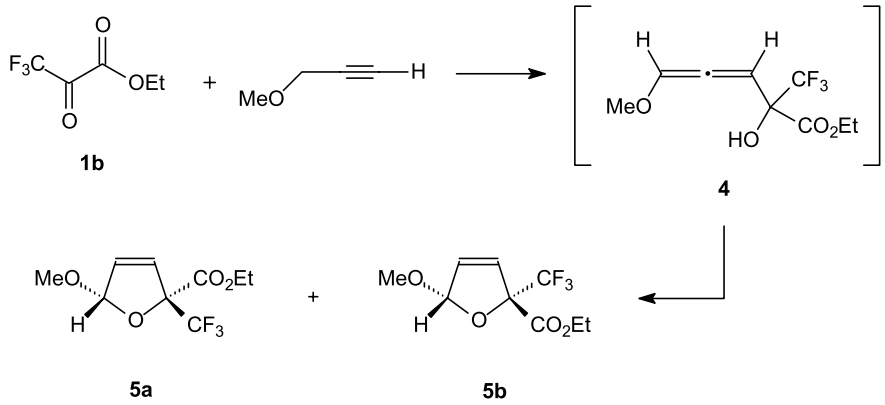
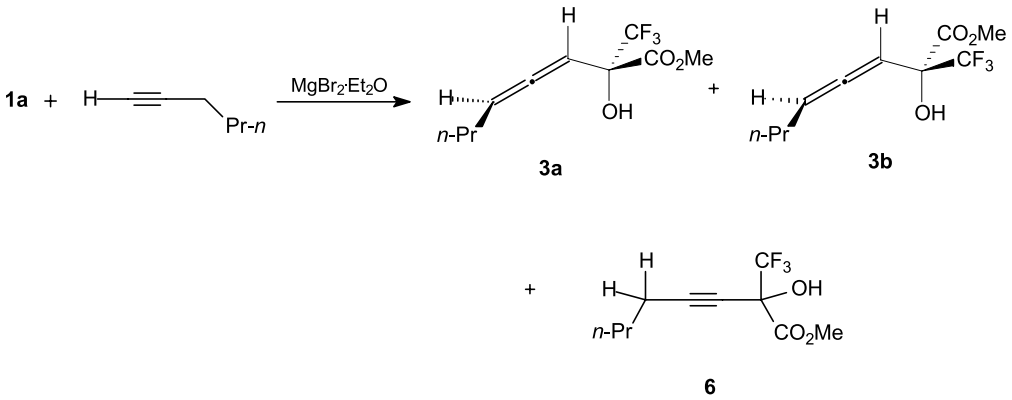


Scheme 2.



Scheme 3.



Scheme 4.

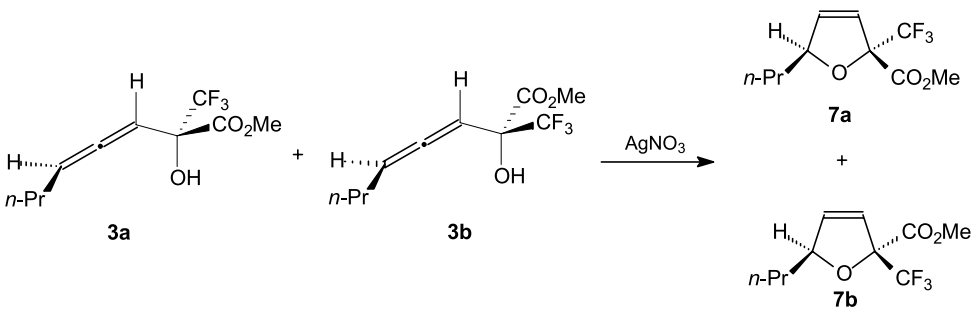
1a with hex-1-yne on addition of $BF_3{\cdot}Et_2O$, $TiCl_4$, $SnCl_4$, $AlCl_3$ were unsuccessful. Complex reaction mixtures were obtained. However, addition of a mixture of hex-1-yne and **1a** to a suspension of $MgBr_2{\cdot}Et_2O$ (3 equiv.) in CH_2Cl_2 at −78°C, followed by warming up the reaction mixture to rt gave product **3** as a 8:1 mixture of diastereomers (88% ds).

Besides the two diastereomeric allenylcarbinols **3a/3b**, we detected the third compound **6** (about 10%) in the crude reaction mixture. It is the product of a methyl trifluoropyruvate insertion into the CH-bond of hex-1-yne (Scheme 4). The structure of product **6** was proved unequivocally by comparison of the spectral data with those obtained for a compound formed by reaction of methyl trifluoropyruvate with $C_4H_9C{\equiv}CMgCl$.[10]

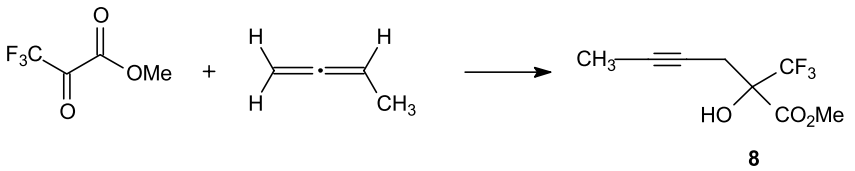
Treatment of a 1:1 diastereomeric mixture of **3a/3b** with $MgBr_2{\cdot}Et_2O$ did not result in an isomerization to give **6**. This proves, that methyl trifluoropyruvate insertion into CH-bond of hex-1-yne proceeds independently under the reaction conditions applied.

Since allenylcarbinols undergo a stereospecific cyclization to give 2,5-dihydrofurans in the presence of catalytic amounts of $AgNO_3$ or $AgBF_4$,[7b,11] configuration of compounds **3a/3b** can be determined on the basis of the configuration of their cyclized products.

Therefore, a 8:1 mixture of diastereomeric allenylcarbinols **3** from the $MgBr_2{\cdot}Et_2O$-promoted reaction was enriched by column chromatography to a 12:1 mixture which was then cyclized on treatment with catalytic amounts of $AgNO_3$ in acetone–water to give 2,5-dihydrofurans **7** (Scheme 5). We obtained a 1:12 mixture of 2,5-dihydrofurans **7a/7b** in 90% yield. ^1H, ^{19}F NOE experiments confirmed a *cis* relationship between the C(2)–CF_3 group and C(5)-*n*–C_3H_7 for the major diastereomer which therefore is assigned structure **7b** showing (*RS*,*SR*)-configuration. Consequently, the major



Scheme 5.



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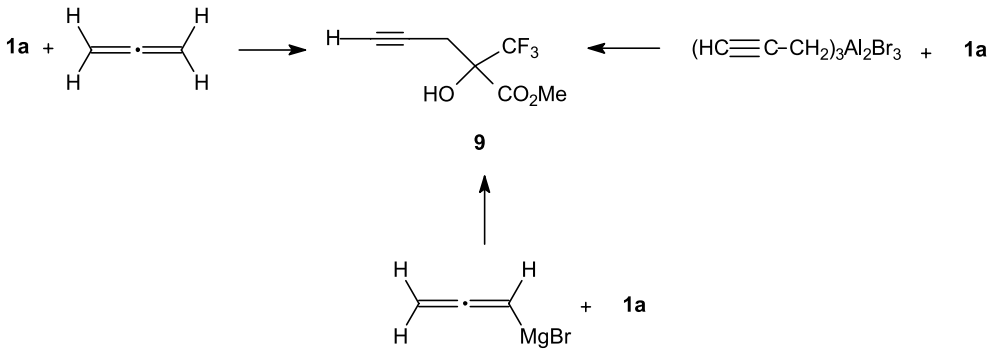
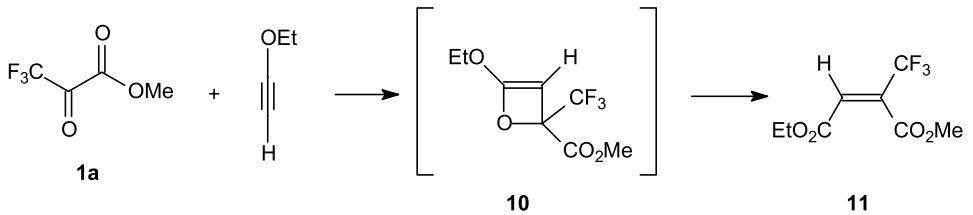


Scheme 7.



Scheme 8.

diastereomer of the $MgBr_2$-promoted reaction **3b** has (*RS*,*SR*)-configuration.

Another type[12] of carbonyl-yne reaction—the reaction of methyl trifluoropyruvate with allenes—was also investigated (Scheme 6). We found, that ketone **1a** is transformed into product **8** on heating with 1,2-butadiene at 100°C for 24 h in 78% yield. According to ^{19}F NMR and GCMS data, **8** was the only reaction product. The alternative reaction pathway, isomerization of 1,2-butadiene to 1,3-butadiene, followed by Diels–Alder reaction[13] with methyl trifluoropyruvate was not observed.

Reaction of **1a** with allene at 80°C gave the yne product **9** in less than 30% yield. The tendency of compound **9** to polymerize at elevated temperatures is a plausible explanation for the low yields of this reaction. Nevertheless, we found, that product **9** is available on the reaction of ketone **1a** with propargyl aluminium sesquibromide in 80% yield (Scheme 7). According to ^{19}F NMR and GCMS data, compound **9** is the only reaction product formed. We did not observe formation of the isomeric allenic product **2** in this transformation. Compound **9** can be also obtained on reaction of ketone **1a** with allenyl magnesium bromide.

Reactions of methyl trifluoropyruvate with acetylenes without propargyl hydrogen atoms proceed according to a fundamentally different mechanism. **1a** reacts with ethoxyacetylene to give exclusively the diester of trifluoromethylmaleinic acid **11** in 65% yield (Scheme 8). The

corresponding derivative of trifluoromethylfumaric acid could not be detected. ^{1}H, ^{19}F NOE experiments and comparison of ^{19}F and ^{1}H NMR data with data given in the literature[14] confirmed unequivocally the structure of compound **11** as a derivative of maleinic acid. The formation of oxete **10** as an intermediate of the reaction could not be detected on monitoring the reaction at rt by ^{19}F NMR spectroscopy. However, from the reaction of hexafluoroacetone[15a] and nitropentafluoroacetone[15b] with ethoxyacetylene the corresponding oxetes[16] have been isolated and characterized. The ring stabilizing effect of a geminal pair of trifluoromethyl groups in valence tautomeric equilibria, like 2,2-bis(trifluoromethyl)-2H-thiazete⇆*N*-thioacyl hexafluoroacetoneimine, is well documented.[17] Doubtlessly, the transformation **1a→11** represents a two step reaction sequence consisting of a [2+2] cycloaddition reaction followed by an electrocyclic ring opening. From the two modes of disrotatory ring openings one seems to be energetically favored.

3. Experimental

3.1. General

Melting points were determined on a Boetius heating table. IR spectra were obtained with a FTIR spectrometer (Genesis ATI Mattson/Unicam). ^{1}H NMR spectra were recorded with VARIAN Gemini 2000 spectrometers at 200 and 300 MHz. Chemical shifts are reported in ppm relative to tetramethylsilane (TMS) in $CDCl_3$; *J* values are given in Hertz (Hz). ^{13}C NMR spectroscopy was performed at 50 and 75 MHz. ^{19}F NMR spectra were recorded at 188 and 282 MHz with trifluoroacetic acid (TFA) as an external standard. ^{1}H, ^{19}F NOE spectra were recorded with a BRUKER DRX-600 at 600 MHz (H^{1}) and 565 MHz (F^{19}). For flash chromatography, silica gel (32–63 μm) was used with solvent systems given in the text. Organic solvents were dried and distilled prior to use.

3.1.1. Methyl 2-hydroxy-2-trifluoromethylpenta-3,4-dienoate (2). To **1a** (5.0 g, 32 mmol) in a glass tube was added methyl acetylene (2.7 g, 68 mmol) at −78°C. The sealed tube was heated for 24 h at 80°C. The volatiles were removed under reduced pressure. The residue was distilled to give product **2** as a colorless oil (4.0 g, 64%); bp 53°C (10 Torr). IR (film): 3500, 1960, 1760 cm^{-1}. ^{1}H NMR (200 MHz, acetone-d_6): δ=3.86 (s, 3H), 5.14 (d, *J*=7.2 Hz, 2H), 5.56 (t, *J*=7.2 Hz, 1H), 6.04 (br, 1H); ^{19}F NMR (188 MHz, acetone-d_6): δ=0.21 (s, 3F); ^{13}C NMR (50 MHz, acetone-d_6): δ=54.6, 77.7 (q, $^{2}J_{CF}$=29.5 Hz), 81.3, 89.6, 125.1 (q, $^{1}J_{CF}$=285 Hz), 169.4, 210.2. Anal. calcd for $C_7H_7F_3O_3$: C, 42.84; H, 3.60. Found: C, 42.65; H, 3.52.

3.1.2. Methyl 2-hydroxy-2-trifluoromethylocta-3,4-dienoate (3). *Thermal reaction*. A mixture of **1a** (1 g, 6.4 mmol) and hex-1-yne (1.6 g, 19.2 mmol) was heated at 80°C in a sealed glass tube for 2 days. The volatiles were removed in vacuo. The residue was purified by column chromatography (eluent: hexanes/ethyl acetate 6:1) to give product **3** as a 1:1 mixture of diastereomers (0.95 g, 62%, colorless oil). IR (film): 3500, 1970, 1750 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.91 (t, *J*=7.4 Hz, 3H), 0.92 (t, *J*=7.4 Hz, 3H), 1.42 (m, 4H), 2.02 (m, 4H), 3.83 (s, 1H), 3.86 (s, 1H), 3.88 (s, 3H), 3.89 (s, 3H), 5.42 (m, 2H), 5.53 (m, 2H); ^{19}F NMR (282 MHz, $CDCl_3$): δ=−0.35 (s, 3F), −0.43 (s, 3F); ^{13}C NMR (75 MHz, $CDCl_3$): δ=13.6, 21.94, 22.00, 30.2, 54.22, 54.26, 75.65 (q, $^{2}J_{CF}$=30.3 Hz), 75.75 (q, $^{2}J_{CF}$=30.3 Hz), 88.09 (q, $^{3}J_{CF}$=1.7 Hz), 88.13 (q, $^{3}J_{CF}$=1.7 Hz), 97.6, 97.8, 122.9 (q, $^{1}J_{CF}$=286 Hz), 169.2 (br), 204.55. HRMS: calcd for $C_{10}H_{13}F_3O_3$ ($M+H^+$) 239.08896. Found: 239.08904.

Catalytic reaction. To a suspension of $MgBr_2{\cdot}OEt_2$ (2.5 g, 9.6 mmol) in CH_2Cl_2 (50 mL) hex-1-yne (0.79 g, 9.6 mmol) and **1a** (0.5 g, 3.2 mmol) were added at −78°C. The reaction mixture was allowed to reach +10°C overnight and was quenched with a saturated NH_4Cl solution (25 mL). The aqueous layer was extracted with CH_2Cl_2 (3×15 mL). The combined organic phase was evaporated under reduced pressure. The GCMS analysis of the residue detected a mixture consisting of product **3** (90%) as a 8:1 mixture of diastereomers and product **6** (10%, preparation, see Section 3). The mixture was purified by column chromatography (eluent: hexanes/ethyl acetate 6:1) to give product **3** as a 12:1 mixture of diastereomers (0.4 g, 52%, colorless oil). ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.92 (t, *J*=7.4 Hz, 3H), 1.43 (m, 2H), 2.02 (m, 2H), 3.87 (s, 1H), 3.89 (s, 3H), 5.42 (m, 1H), 5.53 (q, *J*=6.6 Hz, 1H); ^{19}F NMR (282 MHz, $CDCl_3$): δ=−0.43 (s, 3F); ^{13}C NMR (75 MHz, $CDCl_3$): δ=13.6, 21.94, 30.2, 54.3, 75.65 (q, $^{2}J_{CF}$=30.3 Hz), 88.13 (q, $^{3}J_{CF}$=1.7 Hz), 97.8, 122.9 (q, $^{1}J_{CF}$=286 Hz), 169.2 (br), 204.55.

3.1.3. Ethyl *trans*-2-trifluoromethyl-5-methoxy-2,5-dihydrofuran-2-carboxylate (5a). Compound **1b** (3.0 g, 17.9 mmol) and methyl propargyl ether (4.1 g, 58.5 mmol) were heated in a sealed glass tube at 70°C for 2 days. The volatiles were removed under reduced pressure. The residue was distilled to give a 3:2 mixture of compounds **5a/5b**. The column chromatography on silica gel (eluent: hexanes/ethyl acetate 4:1) gave pure product **5a** (1.33 g, 31%) as a colorless oil. IR (film): 3400, 1755, 1253, 1193, 1068, 985 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.32 (t, *J*=7.2 Hz, 3H), 3.48 (s, 3H), 4.31 (m, 2H), 5.99 (s, 1H), 6.17 (d, *J*=6.0 Hz, 1H), 6.25 (d, *J*=6.0 Hz, 1H); ^{19}F NMR (282 MHz, $CDCl_3$): δ=1.13 (s, 3F); ^{13}C NMR (50 MHz, $CDCl_3$): δ=14.0, 54.9, 62.8, 90.9 (q, $^{2}J_{CF}$=31 Hz), 111.3, 122.6 (q, $^{1}J_{CF}$=283 Hz), 127.7, 133.2, 165.3. HRMS: calcd for $C_9H_{11}F_3O_4$ ($M+H^+$) 263.05016. Found: 263.05030.

3.1.4. Methyl 2-hydroxy-2-trifluoromethyloct-3-ynoate (6). To the solution of hex-1-yne (0.57 g, 6.92 mmol) in THF (50 mL) MeMgBr (1.7 mL, 5.13 mmol; 3 M solution in ether) was added at rt. The reaction mixture was stirred at the same temperature for 1.5 h. The solution was cooled down to −78°C and **1a** (0.8 g, 5.13 mmol) was added dropwise. The reaction mixture was allowed to reach +10°C overnight, then it was quenched with a saturated NH_4Cl solution (50 mL) and extracted with CH_2Cl_2 (3×15 mL). The combined organic phase was dried with $MgSO_4$. The volatiles were removed under reduced pressure. The residue was purified by column chromatography (eluent: hexanes/ethyl acetate 5:1) to give product **6** as a colorless oil (0.8 g, 66%). IR (film): 3500, 2260, 1755 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ=0.89 (t, *J*=6.8 Hz, 3H), 1.45 (m,

4H), 2.25 (t, J=6.8 Hz, 2H), 3.95 (s, 3H), 4.13 (s, 1H); ^{19}F NMR (188 MHz, $CDCl_3$): δ=−2.82 (s, 3F); ^{13}C NMR (50 MHz, $CDCl_3$): δ=13.6, 18.5, 21.9, 30.0, 55.1, 71.4, 71.7 (q, $^2J_{CF}$=34 Hz), 89.5, 121.8 (q, $^1J_{CF}$=286 Hz), 167.4. HRMS: calcd for $C_{10}H_{13}F_3O_3$ (M+Na^+) 261.07090. Found: 261.070103.

3.1.5. Methyl 2-trifluoromethyl-5-(*n*-propyl)-2,5-dihydrofuran-2-carboxylate (7). A mixture of **3** (12:1 mixture of diastereomers, 100 mg, 0.42 mmol), $AgNO_3$ (16 mg, 0.097 mmol) and K_2CO_3 (32 mg, 0.324 mmol) in 3 mL of acetone–water (2:1) was stirred in the dark for 48 h at rt. The reaction mixture was taken up in ether (10 mL), washed with a NaCl solution (5 mL) and dried over $MgSO_4$. The volatiles were removed under reduced pressure to give product **7** as a 12:1 mixture of *cis*- and *trans*-isomers. Yield: (99 mg, 90%).

The spectroscopic data are given for the major *cis*-isomer (**7b**). IR: 3400, 1760, 1260, 1200 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.99 (t, J=7.5 Hz, 3H), 1.46 (m, 2H), 1.62 (m, 2H), 3.86 (s, 3H), 5.15 (m, 1H), 5.87 (dd, J=2.2, 6.0 Hz, 1H), 6.27 (dd, J=0.6, 6.0 Hz, 1H); ^{19}F NMR (282 MHz, $CDCl_3$): δ=2.82 (s, 3F); ^{13}C NMR (50 MHz, $CDCl_3$): δ=14.1, 18.9, 37.4, 53.3, 89.8, 91.7 (q, $^2J_{CF}$=31 Hz), 121.7, 122.5 (q, $^1J_{CF}$=283 Hz), 137.6, 167.3. HRMS: calcd for $C_{10}H_{13}F_3O_3$ (M+Na^+) 261.07090. Found: 261.07088.

3.1.6. Methyl 2-hydroxy-2-trifluoromethylhex-4-ynoate (8). Compound **1a** (5.8 g, 38 mmol) and 1,2-butadiene (2.0 g, 37 mmol) were heated in a sealed glass tube at 100°C for 24 h. The volatiles were removed under reduced pressure. The residue was purified by distillation to give compound **8** (6.1 g, 78%, colorless oil); bp 77°C (10 Torr). IR (film): 3500, 2260, 1760 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.78 (s, 3H), 2.74 (d, J=12.4 Hz, 1H), 2.90 (d, J=12.3 Hz, 1H), 3.95 (s, 3H); ^{19}F NMR (188 MHz, $CDCl_3$): δ=−0.13 (s, 3F); ^{13}C NMR (50 MHz, $CDCl_3$): δ=3.0, 23.1, 54.1, 70.1, 77.1 (q, $^2J_{CF}$=30 Hz), 79.6, 122.6 (q, $^1J_{CF}$=285 Hz), 168.9. Anal. calcd for $C_8H_9F_3O_3$: C, 45.72; H, 4.32; F, 27.12. Found: C, 45.52; H, 4.32; F, 26.79.

3.1.7. Methyl 2-hydroxy-2-trifluoromethyl-pent-4-ynoate (9). *Method 1*. To **1a** (5 g, 32 mmol) in a glass tube allene (2.7 g, 68 mmol) was added at −78°C. The sealed tube for 24 h was added at 80°C. The volatiles were removed under reduced pressure. The residue was distilled to give product **9** as a colorless oil (1.9 g, 30%); bp 35°C (0.2 Torr).

Method 2. To a suspension of Al (3.66 g, 30.77 mmol) in ether (80 mL) a pinch of $HgCl_2$ was added under Ar. The mixture was stirred under reflux for 30 min. To the boiling reaction mixture propargyl bromide (0.83 g, 30.8 mmol) was added dropwise. The mixture was heated under reflux for 2 h. The aluminate solution was filtered off under Ar from the excess of Al. The grew solution was cooled down to −78°C and **1a** (3.0 g, 19.2 mmol) in ether (2 mL) was added dropwise. The reaction mixture was stirred overnight and quenched with saturated NH_4Cl (50 mL) at −78°C. The mixture was allowed to reach rt and extracted with CH_2Cl_2 (3×15 mL). The organic layer was dried with Na_2SO_4. The volatiles were removed under reduce pressure to give pure compound **9** as light-yellow oil (3.3 g, 77.5%).

Method 3. Solution of allenylmagnesium bromide[18] was prepared from Mg (1.2 g, 48.8 mmol) and propargyl bromide (4.3 g, 36.2 mmol) in the presence of catalytic amount of $HgCl_2$. The solution contains about 0.5 equiv. of the required allenylmagnesium bromide in ether (50 mL). To this solution **1a** (3.0 g, 17.65 mmol) was added dropwise at −60°C. The reaction was stirred for 2 h and quenched with a saturated NH_4Cl solution (50 mL). The aqueous layer was extracted with CH_2Cl_2 (3×15 mL) and the combined organic extracts were dried with Na_2SO_4. The volatiles were removed under reduced pressure to give pure compound **9** as light-yellow oil (3.2 g, 80%). IR (film): 3400, 2030, 1750, 1210 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ=2.06 (t, J=2.6 Hz, 1H), 2.78 (dd, ^2J=15.6 Hz, ^4J=2.6 Hz, 1H), 2.94 (dd, ^2J=15.6, 2.6 Hz, 1H), 3.93 (s, 3H), 4.14 (s, 1H); ^{19}F NMR (188 MHz, $CDCl_3$): δ=−2.12 (s, 3F); ^{13}C NMR (50 MHz, $CDCl_3$): δ=24.0, 54.7, 72.3, 76.0, 76.9 (q, $^2J_{CF}$=30 Hz), 122.8 (q, $^1J_{CF}$=286 Hz), 168.8. HRMS: calcd for $C_7H_7F_3O_3$ (M+Na^+) 219.02395. Found: 219.02402.

3.1.8. 4-Ethyl 1-methyl 2-trifluoromethylmaleinate (11). To the solution of **1a** (0.6 g, 3.85 mmol) in CH_2Cl_2 (30 mL) the solution of ethynyl ethyl ether (0.54 g, 3.85 mmol, 50% solution in hexane) was added dropwise at −78°C. Stirring was continued for 4 h (reaction control by TCL, hexanes/ethyl acetate 5:1). The volatiles were removed in vacuo. The residue was purified by column chromatography to give compound **11** as a colorless oil (0.57 g, 66%). IR (film): 2990, 2960, 1740, 1660 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ=1.32 (t, J=7.4 Hz, 3H), 3.89 (s, 3H), 4.29 (q, J=7.4 Hz, 2H), 6.67 (q, J~1 Hz, 1H); ^{19}F NMR (188 MHz, $CDCl_3$): δ=10.79 (d, 3F); ^{13}C NMR (50 MHz, $CDCl_3$): δ=14.0, 53.3, 62.3, 120.9 (q, $^1J_{CF}$=274 Hz), 130.3 (q, $^3J_{CF}$=5.3 Hz), 133.4 (q, $^2J_{CF}$=33.3 Hz), 161.6, 163.2. HRMS: calcd for $C_8H_9F_3O_4$ (M+Na^+) 249.03451. Found: 249.03461.

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