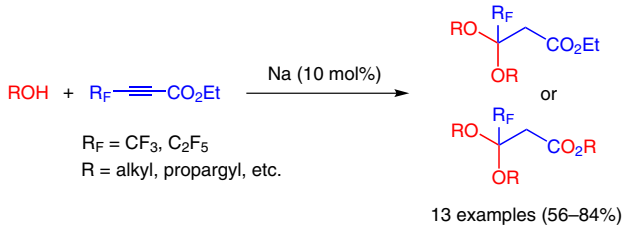
Synthesis E. Ndong et al. Paper

Regioselective Synthesis of α-Perfluoroalkylated Ketals via Double Michael Addition of Alcohols to Activated Alkynes

Ella Ndong[a]
Guy Judicael[a]
Jean Luc Parrain[b]
Mohamed Abarbri*[a]

[a] Laboratoire d'Infectiologie et Santé Publique (UMR 1282), Equipe Recherche et Innovation en Chimie Médicinale, Faculté des Sciences, Parc de Grandmont, 37200 Tours, France
mohamed.abarbri@univ-tours.fr
[b] Aix Marseille Université, Centrale Marseille, CNRS, iSm2 UMR 7313, 13397 Marseille, France



Received: 11.02.2015
Accepted after revision: 16.04.2015
Published online: 17.06.2015
DOI: 10.1055/s-0034-1380753; Art ID: ss-2015-z0103-op

Abstract An efficient method was developed for the synthesis of alkyl 3,3-dialkoxy-3-(perfluoroalkyl)propanoates from ethyl 3-(perfluoroalkyl)propynoates and alcohols using a base-catalyzed double Michael addition reaction (which was accompanied by transesterification in the case of MeOH, EtOH, PrOH, and BuOH). This method provides easy access to the product α-perfluoroalkyl ketals with reasonable to good yields with total regioselectivity. This procedure does not require the use of expensive supplementary additives for the preparation of α-perfluoroalkyl ketals which are very sensitive to acidic conditions.

Key words hydroalkoxylation, Michael addition, fluorinated alkyne, sodium catalyst, perfluorinated ketals

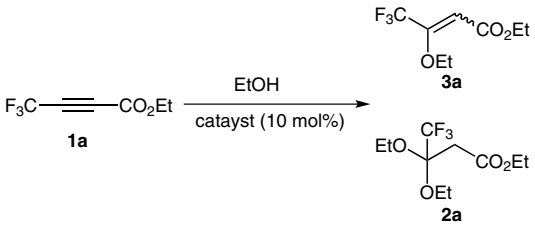
Hydroalkoxylation of alkynes by the addition of alcohols is one of the most economical methods to access vinyl ethers and ketals directly.[1] Although extensive methods have been developed for the intramolecular hydroalkoxylation of alkynes,[2] few synthetic studies have been published on the intermolecular hydroalkoxylation of alkynes. In particular, such hydroalkoxylations were performed using different metal catalysts, such as rhodium,[3] palladium,[4] silver,[5] iridium,[6] platinum,[7] and gold(I) complexes.[8] In the case of ethyl propynoate, Bertz et al.[9] described the preparation of ethyl 3,3-diethoxypropanoate by copper(I) triflate catalyzed addition of ethanol to ethyl propynoate where the presence of the intermediate ethyl 3-ethoxyacrylate was found to depend on the reaction conditions. The β-ketal was obtained as the sole product when the reaction was performed with copper(II) sulfate in refluxing ethanol. In general, the reports have shown that the hydroalkoxylation reaction of ethyl propynoate provided only vinyl enol ethers that are sufficiently stable to avoid a second addition of alcohol.[10] Despite the work performed in this area, the intermolecular addition of alcohols to alkynes under mild conditions is still rare and the simplicity and the high-atom economy of such hydroalkoxylations are highly desirable. In this work, we wish to demonstrate that the introduction of strong electron-withdrawing substituents (e.g., perfluoroalkyl) into an alkyne favors the double hydroalkoxylation under basic conditions providing ketals. Moreover, and despite numerous reports, the acid-catalyzed formation of α-perfluoroalkyl ketals from the corresponding ketones is somewhat difficult since the perfluoroalkyl group strongly stabilizes the ketone hydrate and hemiacetal forms.[11]

To overcome the low reactivity of perfluoroketones under acidic activation, the corresponding acetals were prepared under basic conditions from halogeno alcohols.[11a,12] Nevertheless, under these conditions, only the formation of cyclic acetals was reported and more sophisticated methods using orthoformate,[13] Mitsonobu's conditions,[14] or phosphorus reagents[15] are required to provide acyclic α-perfluoroalkyl acetals.

We report here new direct access to α-perfluoroalkyl ketals by double conjugate addition of alcohols to ethyl 3-(perfluoroalkyl)propynoates using sodium metal as a catalyst. To the best of our knowledge, there has been no report of metal-catalyzed intermolecular hydroalkoxylation of alkynes **1**, and only a few reports in this field of the synthesis of α-perfluoroalkyl ketals.[16] Moreover, the incorporation of a fluoroalkyl group in organic compounds plays an important role in the search for new active pharmaceutical compounds.[17] Indeed, the trifluoromethyl moiety is known to influence metabolic stability, binding activity, and lipophilicity.[18]

The reaction of ethyl 4,4,4-trifluorobut-2-ynoate (**1a**) with ethanol was selected to optimize the reaction conditions of the double conjugate addition (Table 1). First, we examined the use of a variety of metal catalysts [CuI, $AgOCOCF_3$, $ZnCl_2$, $CuCl_2$, $AuCl_3$, $Mg(OTf)_2$, and $FeCl_3$] to pro-

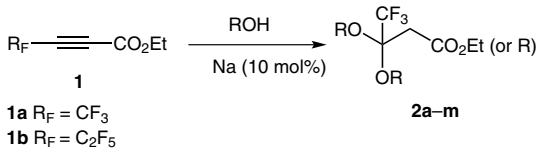
Table 1 Effects of the Catalyst on the Hydroalkoxylation of **1a**



Entry	Catalyst (10 mol%)	Product	Ratio[a] *E*/*Z*	Yield (%)
1	CuI	**3a**	0:100	50
2	$AgOCOCF_3$	**3a**	5:95	68
3	$ZnCl_2$	**3a**	43:57	49
4	$CuCl_2$	**3a**	50:50	45
5	$AuCl_3$	**3a**	6:94	70
6	$Mg(OTf)_2$	**3a**	40:60	65
7	DABCO	**3a**	88:12	88
8	Et_3N	**3a**	95:5	62
9	$FeCl_3$	**3a**	52:48	**63**
10	Na	**2a**	–	**84**
11[b]	Na	**3a**	63:27	**52**
12[c]	Na	**2a**	–	**80**

[a] Determined by ^1H NMR.
[b] Na (2 mol%) was used.
[c] A stoichiometric amount of Na was used.

mote this hydroalkoxylation reaction, and in all cases these reactions led exclusively to isomer mixtures of vinyl ether **3a** without the formation of ketal **2a** (entries 1–6, 9). Using bases such as DABCO or Et_3N also led to the same result (entries 7 and 8). Upon optimization, we found that sodium was the most effective catalyst. In fact, when the hydroalkoxylation of fluorinated alkyne **1a** was performed with excess ethanol using 10 mol% sodium at room temperature for three hours, the double Michael addition gave solely ketal **2a** in 84% yield (entry 10). The formation of two C–O bonds took place regioselectively at the β-position of **1a**, and no ketal in the α-position of **1a** was detected. Further optimization of the conditions revealed that decreasing the amount of sodium to 2 mol% under the same reaction conditions was not efficient and gave the monoaddition product **3a** (entry 11). When a stoichiometric amount of sodium was used, no significant difference in yield of ketal **2a** was observed (compare entries 10 and 12).



Scheme 1 Hydroalkoxylation of **1**

The scope of this reaction was investigated using a variety of alcohols for the regioselective synthesis of ketals (Scheme 1). The results are summarized in Table 2.

Table 2 Synthesis of Perfluoroalkylated Ketals **2a–m**

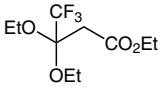
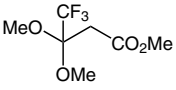
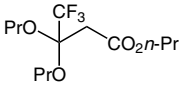
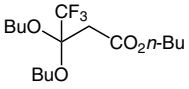
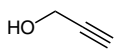
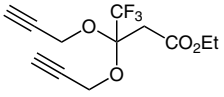
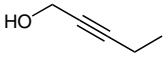
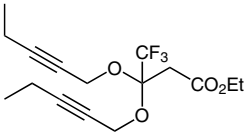
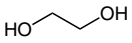
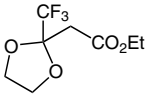
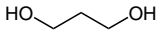
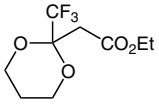
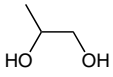
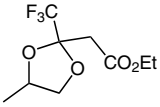
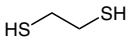
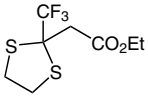
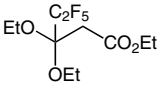
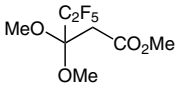
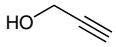
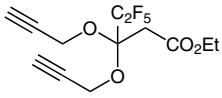
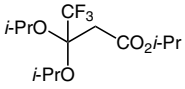
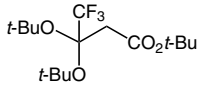
Entry	R_F	Alcohol	Product		Yield (%)
1	CF_3	EtOH		**2a**	84
2	CF_3	MeOH		**2b**	73
3	CF_3	PrOH		**2c**	71
4	CF_3	BuOH		**2d**	62
5	CF_3			**2e**	73

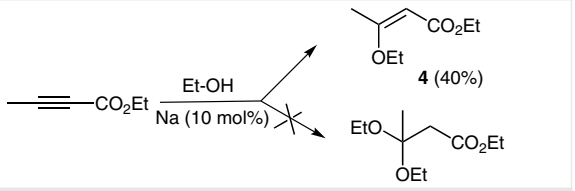
Table 2 (continued)

Entry	R_F	Alcohol	Product		Yield (%)
6	CF_3			**2f**	69
7	CF_3			**2g**	68
8	CF_3			**2h**	56
9	CF_3			**2i**	57
10	CF3			**2j**	60
11	C_2F_5	EtOH		**2k**	71
12	C_2F_5	MeOH		**2l**	68
13	C_2F_5			**2m**	70
14	CF_3	*i*-PrOH		**2n**	0
15	CF_3	*t*-BuOH		**2o**	0

As shown in Table 2, sodium metal was found to catalyze the double conjugate addition of a variety of alcohols to ethyl 3-(perfluoroalkyl)propynoate **1** to produce the corresponding α-perfluoroalkyl ketals **2a**–**m**. The reaction proceeded smoothly with reasonable to good yields, and was highly regioselective. A range of primary alcohols such as methanol, ethanol, propanol, and butanol underwent double Michael reactions, providing perfluoroalkylated 3,3-dialkoxypropanoates **2a**–**d**,**k**,**l** in 62–84% yields (entries 1–4, 11, and 12); the alcohols were used as both reactant and solvent, hence transesterification also took place. Moreover, no traces of vinyl ethers resulting from monoaddition were detected. The use of a stoichiometric amount of alcohol does not prevent the transesterification, and leads to a mixture of several products. The use of secondary and bulkier alcohols in this reaction gave no product (entries 14 and 15). However, the use of a diol as substrate containing both primary and secondary alcohol functions such as propane-1,2-diol provided the double conjugate addition adduct **2i** as a mixture of diastereomers [57% yield in a ratio ca. 60:40 (entry 9)]. This result showed that the addition of the second alkoxide was facilitated by the intramolecular process,

certainly for entropic reasons. Propargyl alcohols also reacted effectively to provide good yields of the expected products **2e**,**f**,**m** (entries 5, 6, and 13) and, interestingly, no transesterification was observed. Note that in the case of propargyl alcohols, the use of 1,4-diazabicyclo[2.2.2]cyclooctane (DABCO) at 40 °C instead of sodium catalyst led to the formation of fluorinated furans, as previously reported.[19] Propynoate **1a** was directly converted into cyclic ketal **2g** on treatment with one equivalent of ethane-1,2-diol (entry 7). Moreover, the use of propane-1,3-diol readily provided 1,3-dioxolane **2h** in 56% yield (entry 8); the extension of this reaction to ethane-1,2-dithiol successfully gave 1,3-dithiolane **2j** in 60% yield (entry 10).

In order to examine the influence of the fluoroalkyl group under these conditions, ethanol was added to ethyl but-2-ynoate and this provided vinyl ether **4** only in 40% isolated yield, without the formation of the ketal (Scheme 2). This result shows the important role of the presence of the fluorinated group in the formation of ketals, thus facilitating the double conjugate addition of the second alkoxide to **1**, providing the exclusive formation of ketals **2a**–**m**.



Scheme 2 Hydroalkoxylation of ethyl but-2-ynoate

Finally, we found that the perfluoroalkyl ketals **2a**–**m** are extremely unstable under mildly acidic conditions, such as in the presence of silica gel, and they decompose to form the vinyl ether, ethyl 4,4,4-trifluoro-3-oxobutanoate, the starting material, and unidentified products. To avoid such decomposition on silica gel, the obtained ketals were, therefore, purified on a neutral alumina column.

In summary, we have developed an efficient, convenient method for the regioselective double conjugate addition of alcohols to ethyl 3-(perfluoroalkyl)propynoates to give easy access to α-perfluorinated ketals. The processes reported are operationally simple and atom-economical, and employ mild reaction conditions. Extending the reaction conditions to other substrates and the conversion of the double Michael products into other potentially useful compounds are underway in our laboratory.

All reactions were carried out under argon atmosphere. Alcohols were obtained from commercial sources and were used without further purification. Et_2O was dried and freshly distilled from Na/benzophenone. Column chromatography was performed using Merck neutral alumina (150 mesh).^{1}H (300 MHz), ^{13}C (75 MHz), and ^{19}F (282 MHz) NMR spectra were obtained using a Bruker Avance 300 spectrometer relative to residual $CHCl_3$ (δ = 7.26) or DMSO (δ = 2.50) signals. HRMS-ESI were run on a hybrid tandem quadrupole/time-of-flight (Q-TOF) instrument, equipped with a pneumatically assisted electrospray (Z-spray) ion source (Micromass, Manchester, U.K.) operated in positive mode.

α-Perfluoroalkyl Ketals 2a–m; General Procedure

To a 25-mL dry schlenk flask under argon was added alcohol (36.0 mmol, 20 equiv) followed by the careful introduction of Na (4 mg, 0.18 mmol, 10 mol%). After homogenization of the solution, **1a** or **1b** (1.8 mmol, 1 equiv) was added via syringe. The mixture was stirred overnight at r.t. The solvent was evaporated in vacuo and the crude product was purified on neutral alumina (Et_2O) to give the products **2a**–**m** in good yields.

Ethyl 3,3-Diethoxy-4,4,4-trifluorobutanoate (2a)

Colorless oil; yield: 389 mg (84%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.12 (q, *J* = 6.0 Hz, 2 H), 3.82–3.77 (m, 2 H), 3.64–3.59 (m, 2 H), 2.80 (s, 2 H), 1.25 (t, *J* = 6.0 Hz, 3 H), 1.23 (t, *J* = 6.0 Hz, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.9, 120.7 (q, *J* = 288.8 Hz), 97.6 (q, *J* = 30.8 Hz), 61.0, 58.7 (2 C), 38.4, 15.0 (2 C), 14.0.

^{19}F NMR (282 MHz, $CDCl_3$): δ = –78.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_{18}F_3O_4$: 259.1157; found: 259.1153 (0.6 ppm).

Methyl 4,4,4-Trifluoro-3,3-dimethoxybutanoate (2b)

Colorless oil; yield: 260 mg (73%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.70 (s, 3 H), 3.44 (s, 6 H), 2.82 (s, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.8, 124.0 (q, *J* = 289.5 Hz), 97.8 (q, *J* = 30.0 Hz), 52.2, 50.7 (2 C), 37.6.

^{19}F NMR (282 MHz, $CDCl_3$): δ = –77.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_7H_{12}F_3O_4$: 217.06877; found: 217.07082 (11.9 ppm).

Propyl 4,4,4-Trifluoro-3,3-dipropoxybutanoate (2c)

Yellow oil; yield: 351 mg (71%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.04 (t, *J* =6.0 Hz, 2 H), 3.71–3.66 (m, 2 H), 3.53–3.50 (m, 2 H), 2.83 (s, 2 H), 1.68–1.59 (m, 6 H), 0.95 (t, *J* = 6.0 Hz, 3 H), 0.92 (t, *J* = 6.0 Hz, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.7, 120.8 (q, *J* = 289.9 Hz), 97.4 (q, *J* = 30.0 Hz), 66.6, 64.6 (2 C), 38.4, 23.0 (2 C), 22.0, 10.7 (2 C), 10.5.

^{19}F NMR (282 MHz, $CDCl_3$): δ = –77.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{24}F_3O_4$: 301.16267; found: 301.16510 (0.05 ppm).

Butyl 3,3-Dibutoxy-4,4,4-trifluorobutanoate (2d)

Yellow oil; yield: 345 mg (62%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.07 (t, *J* = 6.0 Hz, 2 H), 3.74–3.53 (m, 4 H), 2.81 (s, 2 H), 1.62–1.39 (m, 6 H), 1.38–1.33 (m, 6 H), 0.92 (t, *J* = 6.0 Hz, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.7, 120.8 (q, *J* = 289.9 Hz), 97.9 (q, *J* = 30.0 Hz), 64.9, 62.8 (2 C), 38.4, 31.3 (2 C), 30.6, 19.3 (2 C), 19.1, 13.9 (2 C), 13.7.

^{19}F NMR (282 MHz, $CDCl_3$): δ –77.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{30}F_3O_4$: 343.20962; found: 343.20910 (0.1 ppm).

Ethyl 4,4,4-Trifluoro-3,3-bis(prop-2-ynyloxy)butanoate (2e)

Colorless oil; yield: 336 mg (73%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.59 (dd, *J* = 15.0, 3.0 Hz, 2 H), 4.38 (dd, *J* = 15.0, 3.0 Hz, 2 H), 4.19 (q, *J* = 6.0 Hz, 2 H), 2.90 (s, 2 H), 2.48 (t, *J* = 3.0 Hz, 2 H), 1.27 (t, *J* = 6.0 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.2, 122.0 (q, *J* = 290.2), 98.5 (q, *J* = 31.5), 78.3 (2 C), 75.4 (2 C), 61.5, 52.4 (2 C), 37.8, 13.6.

^{19}F NMR (282 MHz, $CDCl_3$): δ = –78.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{14}F_3O_4$: 279.0840; found: 279.0840 (0.5 ppm).

Ethyl 4,4,4-Trifluoro-3,3-bis(pent-2-ynyloxy)butanoate (2f)

Colorless oil; yield: 308 mg (69%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.53 (dt, *J* = 15.0, 3.0 Hz, 2 H), 4.33 (dt, *J* = 15.0, 3.0 Hz, 2 H), 4.15 (q, *J* = 6.0 Hz, 2 H), 2.88 (s 2 H), 2.27–2.17 (m, 4 H), 1.26 (t, *J* = 6.0 Hz, 3 H), 1.14 (t, *J* = 6.0 Hz, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.6, 122.1 (q, *J* = 281.2 Hz), 98.3 (q, *J* = 26.3 Hz), 88.6 (2 C), 74.1 (2 C), 61.2, 52.7 (2 C), 38.1, 14.0 (2 C), 12.5, 12.4 (2 C).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –78.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{22}F_3O_4$: 335.1470; found: 335.1466 (0.4 ppm).

Ethyl 2-[2-(Trifluoromethyl)-1,3-dioxolan-2-yl]acetate (2g)

Colorless oil; yield: 153 mg (68%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.22–4.17 (m, 4 H), 4.15 (q, *J* = 6.0 Hz, 2 H), 2.87 (s, 2 H), 1.25 (t, *J* = 6.0 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.1, 120.8 (q, *J* = 288.0 Hz), 104.2 (q, *J* = 30.1 Hz), 67.3 (2 C), 60.9, 37.0, 14.0.

^{19}F NMR (282 MHz, $CDCl_3$): δ = –83.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_8H_{12}F_3O_4$: 229.17369; found: 229.06822 (0.02 ppm).

Ethyl 2-[2-(Trifluoromethyl)-1,3-dioxan-2-yl]acetate (2h)

Colorless oil; yield: 124 mg (56%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.12 (q, *J* = 6.0 Hz, 2 H), 4.08–4.02 (m, 4 H), 2.77 (s, 2 H), 1.75–169 (m, 2 H), 1.22 (t, *J* = 6.0 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.3, 121.1 (q, *J* = 291.0), 94.5 (q, *J* = 30.5 Hz), 61.7 (2 C), 60.9, 38.4, 23.6, 14.1.

^{19}F NMR (282 MHz, $CDCl_3$): δ = –78.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_9H_{14}F_3O_4$: 243.20027; found: 243.08374 (–0.54 ppm).

Ethyl 2-[4-Methyl-2-(trifluoromethyl)-1,3-dioxolan-2-yl]acetate (2i)

Colorless oil; yield: 244 mg (57%); mixture of two diastereomer in a ratio ca. 60:40.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_9H_{14}F_3O_4$: 243.20027; found: 243.08374 (–0.54 ppm).

^{1}H NMR (300 MHz, $CDCl_3$): δ (major) = 4.56–4.52 (m, 1 H), 4.17 (q, *J* = 6.0 Hz, 2 H), 3.71–3.61 (m, 2 H), 2.86 (s, 2 H), 1.33 (d, *J* = 6.0 Hz, 3 H), 1.27 (t, *J* = 6.0 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (major) = 167.4, 122.6 (q, *J* = 287.2 Hz), 104.5 (q, *J* = 31.9 Hz), 75.7, 73.1, 61.0, 37.4, 17.4, 14.2.

^{19}F NMR (282 MHz, $CDCl_3$): δ (major) = –83.8.

^{1}H NMR (300 MHz, $CDCl_3$): δ (minor) = 4.34–4.28 (m, 1 H), 4.27–4.21 (m, 2 H), 4.18 (q, *J* = 6.0 Hz, 2 H), 2.90 (s, 2 H), 1.34 (d, *J* = 6.0 Hz, 3 H), 1.28 (t, *J* = 6.0 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (minor) = 167.2, 122.8 (q, *J* = 288.7 Hz), 104.4 (q, *J* = 32.2 Hz), 75.6, 73.5, 61.0, 37.3, 17. 6, 14.1.

^{19}F NMR (282 MHz, $CDCl_3$): δ (minor) = –83.6.

Ethyl 2-[2-(Trifluoromethyl)-1,3-dithiolan-2-yl]acetate (2j)

Colorless oil; yield: 102 mg (60%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.18 (q, *J* = 7.5 Hz, 2 H), 3.40 (s, 4 H), 3.10 (s, 2 H), 1.25 (t, *J* = 7.5 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.7, 126.5 (q, *J* = 277.0 Hz), 66.8 (q, *J* = 28.5 Hz), 61.0, 41.1, 40.2, 13.1.

^{19}F NMR (282 MHz, $CDCl_3$): δ = –73.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_8H_{12}F_3O_2S_2$: 261.30489; found: 261.02263 (0.39 ppm).

Ethyl 3,3-Diethoxy-4,4,5,5,5-pentafluoropentanoate (2k)

Golden oil; yield: 246 mg (71%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.14 (q, *J* = 7.2 Hz, 2 H), 3.84–3.59 (m, 4 H), 2.90 (s, 2 H), 1.24 (t, *J* = 7.2 Hz, 3 H), 1.22 (t, *J* = 7.0 Hz, 6 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 167.5, 118.8 (tq, *J* = 285.0, 34.5 Hz), 115.1 (qt, *J* = 268.5, 35.2 Hz), 98.6 (t, *J* = 22.5), 61.0, 59.4 (2 C), 38.1, 14.8, 13.9 (2 C).

^{19}F NMR (282 MHz, $CDCl_3$): –79.7, –121.1.

HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_{17}F_5O_4Na$: 331.09447; found: 331.09344 (–1.44427 ppm).

Methyl 4,4,5,5,5-Pentafluoro-3,3-dimethoxypentanoate (2l)

Yellow solid; yield: 185 mg (68%); mp 90–92 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.60 (s, 3 H), 3.40 (s, 6 H), 3.04 (s, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.2, 118.3 (tq, *J* = 272.0, 33.2 Hz), 115.2 (qt, *J* = 286.0, 33.3 Hz), 98.9 (t, *J* = 22. 5 Hz), 51.6 (2 C), 51.0, 36.0.

^{19}F NMR (282 MHz, CD_3Cl): δ = –79.1, –120.1.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_8H_{11}F_5O_4Na$: 289.04752; found: 289.04674 (–0.78793 ppm).

Ethyl 4,4,5,5,5-Pentafluoro-3,3-bis(prop-2-ynyloxy)pentanoate (2m)

Yellow oil; yield: 283 mg (70%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.64 (dt, *J* = 15.0, 3.0 Hz, 2 H), 4.43 (dt, *J* = 15, 3.0 Hz, 2 H), 4.18 (q, *J* = 6.0 Hz, 2 H), 2.99 (s, 2 H), 2.49 (t, *J* = 3.0 Hz, 2 H), 1.27 (t, *J* = 6.0 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.6, 118.4 (tq, *J* = 288.7, 34.5 Hz), 114.6 (qt, *J* = 266.2, 36.5 Hz), 99.0 (t, *J* = 23.2 Hz), 78.3 (2 C), 75.4 (2 C), 61.3, 52.7 (2 C), 38.2, 13.8.

^{19}F NMR (282 MHz, $CDCl_3$): δ = –79.6, –121.7.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{13}F_5O_4Na$: 351.06317; found: 351.06221 (–1.17359 ppm).

Acknowledgment

We thank the 'Département d'analyses Chimiques et Médicales' (Tours, France) for chemical analyses.

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1380753.

References

(1) (a) For an exhaustive review, see: Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2004**, *104*, 3079. (b) *Kirk-Othmer Encyclopedia of Chemical Technology*, 4th ed., Vol. 1; Kroschwitz, J. I.; Howe-Grant, M., Eds.; John Wiley & Sons: New York, **1991**, 221.
(2) (a) Castro, C. E.; Stephens, R. D. *J. Org. Chem.* **1963**, *28*, 2163. (b) Castro, C. E.; Gaughan, E. J.; Owsley, D. C. *J. Org. Chem.* **1966**, *31*, 4071. (c) Castro, C. E.; Havlin, R.; Honwad, V. K.; Malte, A.; Mojé, S. *J. Am. Chem. Soc.* **1969**, *91*, 6464. (d) Houpis, I. N.; Choi, W. B.; Reider, P. J.; Molina, A.; Churchill, H.; Lynch, J.; Volante, R. P. *Tetrahedron Lett.* **1994**, *35*, 9355. (e) Chowdhury, C.; Chaudhuri, G.; Guha, S.; Mukherjee, A. K.; Kundu, N. G. *J. Org. Chem.* **1998**, *63*, 1863. (f) Bates, C. G.; Saejueng, P.; Murphy, J. M.; Venkataraman, D. *Org. Lett.* **2002**, *4*, 4727.
(3) Kondo, M.; Kochi, T.; Kakiuchi, F. *J. Am. Chem. Soc.* **2011**, *133*, 32.
(4) (a) Murata, T.; Mizobe, Y.; Gao, H.; Ishii, Y.; Wakabayashi, T.; Nakanao, F.; Tanase, T.; Yano, S.; Hidai, M.; Echizen, I.; Nanikawa, H.; Motomura, S. *J. Am. Chem. Soc.* **1994**, *116*, 3398. (b) Avshu, A.; O'Sullivan, R. D.; Parkins, A. W.; Alcock, N. W.; Countryman, R. M. *J. Chem. Soc., Dalton Trans.* **1983**, 1619.
(5) Kataoka, Y.; Matsumoto, O.; Tani, K. *Chem. Lett.* **1996**, 727.
(6) (a) Messerle, B. A.; Vuong, K. Q. *Organometallics* **2007**, *26*, 3031. (b) Messerle, B. A.; Vuong, K. Q. *Pure Appl. Chem.* **2006**, *78*, 385.
(7) Kataoka, Y.; Matsumoto, O.; Tani, K. *Organometallics* **1996**, *15*, 5246.
(8) (a) Ketcham, J. M.; Biannic, B.; Aponick, A. *Chem. Commun.* **2013**, *49*, 4157. (b) Belting, V.; Krause, N. *Org. Lett.* **2006**, *8*, 4489. (c) Diéguez-Vazquez, A.; Tzschucke, C. C.; Crecente-Campo, J.; McGrath, S.; Ley, S. V. *Eur. J. Org. Chem.* **2009**, 1698. (d) Schulz, M.; Teles, J. H. WO 9721648, **1997**; *Chem. Abstr.* **1997**, *127*, 121499. (e) Teles, J. H.; Brode, S.; Chabanas, M. *Angew. Chem. Int. Ed.* **1998**, *37*, 1415. (f) Fukuda, Y.; Utimoto, K. *J. Org. Chem.* **1991**, *56*, 3729. (g) Fukuda, Y.; Utimoto, K. JP 04095039, **1990**; *Chem. Abstr.* **1992**, *117*, 191330.
(9) Bertz, S. H.; Dabbagh, G.; Cotte, P. *J. Org. Chem.* **1982**, *47*, 2216.
(10) Corma, A.; Ruis, V. R.; Leyva-Pérez, A.; Sabater, M. J. *Adv. Synth. Catal.* **2010**, *352*, 1701.
(11) (a) Reeves, J. T.; Fandrick, D. R.; Tan, Z.; Song, J. J.; Rodriguez, S.; Qu, B.; Kim, S.; Niemeier, O.; Li, Z.; Byrne, D.; Campbell, S.; Chitroda, A.; DeCroos, P.; Fachinger, T.; Fuchs, V.; Gonnella, N. C.; Grinberg, N.; Haddad, N.; Jäger, B.; Lee, H.; Lorenz, J. C.; Ma, S.; Narayanan, B. A.; Nummy, L. J.; Premasiri, A.; Roschangar, F.; Sarvestani, M.; Shen, S.; Spinelli, E.; Sun, X.; Varsolona, R. J.; Yee, N.; Brenner, M.; Senanayake, C. H. *J. Org. Chem.* **2013**, *78*, 3616. (b) Bégué, J. P.; Bonnet-Delpon, D. *Tetrahedron* **1991**, *47*, 3207.
(12) (a) Simmons, H. E. Jr.; Wiley, D. W. *J. Am. Chem. Soc.* **1960**, *82*, 2288. (b) Aubert, C.; Begue, J. P.; Charpentier-Morize, M.; Nee, G.; Langlois, B. *J. Fluorine Chem.* **1989**, *44*, 377. (c) Barbasiewicz, M.; Makosza, M. *Org. Lett.* **2006**, *8*, 3745.
(13) Wulff, G.; Wolf, G. *Chem. Ber.* **1986**, *119*, 1876.
(14) Szabo, D.; Bonto, A.-M.; Koevesdi, I.; Goemoery, A.; Rabai, J. *J. Fluorine Chem.* **2005**, *126*, 639.
(15) Yang, Z.-Y. *J. Org. Chem.* **1995**, *60*, 5696.
(16) (a) Pavlov, A. M.; Chizhov, D. L.; Charushin, V. N. *Russ. J. Org. Chem.* **2005**, *41*, 1449. (b) Yamanaka, H.; Tamura, K.; Funabiki, K.; Fukunishi, K.; Ishihara, T. *J. Fluorine Chem.* **1992**, *57*, 177. (c) Zuczek, C.; Gérardin, C.; Rocca, S.; Thiébaut, S.; Selve, C. *J. Fluorine Chem.* **1999**, *99*, 41. (d) Shcherbakova, I.; Huang, G.; Geoffroy, O. J.; Nair, S. K.; Swierczek, K.; Balandrin, M. F.; Fox, J.; Heaton, W. L.; Conklin, R. L. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2537.
(17) (a) Smart, B. E. *Chem. Rev.* **1996**, *96*, 1555. (b) Banks, R. E.; Smart, B. E.; Tatlow, J. C. *Organofluorine Chemistry: Principle and Commercial Applications*; Plenum Press: New York, **1994**.
(18) (a) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320. (b) Müller, K.; Faeh, C.; Diederich, F. *Science (Washington, D.C.)* **2007**, *317*, 1881.
(19) Chong, Q.; Xin, X.; Wang, C.; Wu, F.; Wang, H.; Shi, J.-C.; Wan, B. *J. Org. Chem.* **2014**, *79*, 2105.