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PAPER

Perfluoroalkylation in flow microreactors: generation of perfluoroalkyllithiums in the presence and absence of electrophiles†

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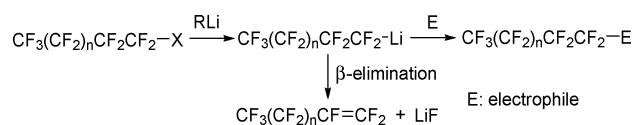
Perfluoroalkyllithiums were effectively generated from perfluoroalkyl halides in the presence and absence of electrophiles using flow microreactor systems. The *in situ* trapping with electrophile is conducted at much higher temperatures than those required for batch macro reactors. The subsequent trapping method is quite effective for highly reactive electrophiles that are not compatible with the lithiation process.

Introduction

Because long chain perfluoroalkyl groups add unique properties to parent molecules, perfluoroalkyl-substituted compounds have received significant research interest from with regard to biological activity and physical functions.[1,2] Recently, fluorous chemistry based on perfluoroalkyl groups serves as a powerful method for strategic separation because the fluorous phase serves as a new phase that is immiscible to both aqueous and organic phases, which is useful for anti-coatings for textiles.[3] In this context, there is a strong demand for synthesizing a variety of organic compounds bearing perfluoroalkyl groups.[4] Radical perfluoroalkylation is very popular because perfluoroalkyl radicals are easily generated from readily available precursors, such as perfluoroalkyl halides.[5] In contrast, the use of perfluoroalkyl anions has been rather limited because of low nucleophilicity and thermal instability.[6] Thermally stable perfluoroalkylmetals, such as perfluoroalkyl zincs and coppers are sometimes not reactive enough toward weak electrophiles.[7] Perfluoroalkyllithiums, which are often prepared by halogen–lithium exchange reactions of perfluoroalkyl halides with alkyllithiums are more reactive, but they readily undergo β-elimination to form perfluoroalkenes (Scheme 1).[8] Meanwhile, flow microreactor methods have received significant interest due to their prominent abilities of reaction control.[9,10,11] Schwalbe *et al.* reported that the generation and reaction of pentafluoroethyllithium with benzophenone could be performed using a microreactor but the yield was not high, although the reaction using a more stable perfluoroethylmagnesium gave high yields.[12] With a wide substrate scope, the development of an efficient

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Scheme 1 The generation of perfluoroalkyllithiums followed by their reactions with electrophiles and the possibility of β-elimination.

method for perfluoroalkylation by perfluoroalkyllithiums avoiding β-elimination is strongly needed.

Recently, we have reported that flow microreactor systems are quite effective for controlling reactions involving highly unstable reactive intermediates.[13] Therefore, we envisaged that flow microreactor systems are also effective for the generation and reactions of fluorine-containing reactive species.[14] In this paper, we show that this is indeed the case. In particular, we report a new method for conducting anionic perfluoroalkylation involving the generation of perfluoroalkyllithiums in the absence of electrophiles and subsequent reactions with highly reactive electrophiles that are not compatible with the generation process.

Results and discussion

We began with the generation of perfluoroalkyllithiums in the presence of electrophiles in flow because this method is popular in batch macro processes.[8] Before using a flow microreactor system, the reaction in a macro batch reactor was examined. A solution of MeLi (0.42 M in Et_2O, 2.25 mL) was added dropwise to a solution of tridecafluorohexyl iodide (0.10 M) and benzaldehyde (0.12 M) in Et_2O (9 mL) at a particular temperature ($T/°C$). After stirring for 1 min, methanol (neat, 3.0 mL) was added dropwise to this mixture. After stirring at T °C for 10 min, the yield of 1-phenyl-2,2,3,3,4,4,5,5,6,6,7,7,7-tridecafluoroheptan-1-ol was determined by GC (gas chromatography). As shown in Table 1, the reaction at −78 °C gave the product in 67% yield but the reaction at higher temperatures, such as 0 °C, caused a decrease in the yield because the β-elimination of tridecafluorohexyllithium took place.

Table 1 The reaction of tridecafluorohexyllithium with benzaldehyde using a conventional batch macro reactor

$$CF_3(CF_2)_4CF_2\text{-I} + \underset{\text{PhCHO}}{} \xrightarrow[\text{2) MeOH}]{\substack{\text{1) MeLi (1.05 equiv)} \\ T\ ^\circ\text{C, 1 min}}} C_6F_{13}\overset{\text{OH}}{\underset{}{\text{CH}}}\text{Ph}$$

$T/^\circ\text{C}$	Yield (%)[a]
−78	67
0	46

[a] GC yields using an internal standard.

Next, a flow microreactor system consisting of two stainless steel (SUS304) T-shaped micromixers (**M1** and **M2)** and two stainless steel (SUS316) microtube reactors (**R1** and **R2)** was used (Fig. 1). The reactions could be conducted at 0 °C, although much lower temperatures, such as −78 °C, are required to avoid the decomposition of perfluoroalkyllithium intermediates in batch processes.[15] The flow method is applicable to perfluoroalkyl iodides of various chain lengths and various electrophiles, including aldehydes, ketones and isocyanates (Table 2). It is also noteworthy that the products were obtained in good yields based on perfluoroalkyl halides using 1.2 equiv. of electrophiles, although batch macro processes are often carried out using an excess amount of perfluoroalkyl halides and the yields are reported based on electrophiles.
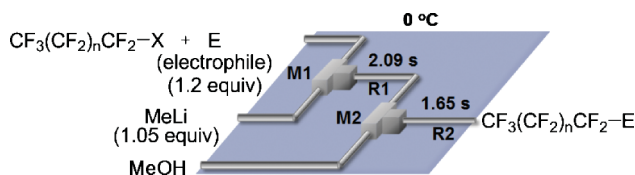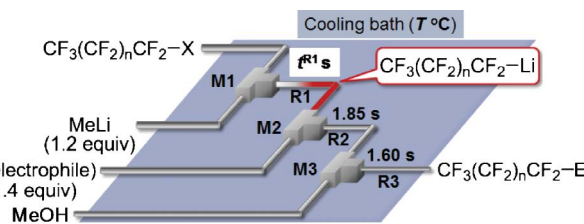

Fig. 1 A flow microreactor system for perfluoroalkylation by the generation of perfluoroalkyllithiums in the presence of electrophiles. T-shaped micromixers: **M1**(250 μm) and **M2** (500 μm), microtube reactors: **R1** ($\phi = 1000$ μm, $L = 50$ cm) and **R2** ($\phi = 1000$ μm, $L = 50$ cm). Flow rate of a mixture solution of a perfluoroalkyl halide (0.10 M) and an electrophile (0.12 M) in Et$_2$O: 9.00 mL min^{-1}; flow rate of a solution of MeLi (0.42 M) in Et$_2$O: 2.25 mL min^{-1}; flow rate of methanol: 3.00 mL min^{-1}.

It should be noted that the use of highly reactive electrophiles, such as trimethylsilyl triflate and chlorotributylstannane, gave rise to very low yields of the desired products, which is presumably because the reactions of MeLi with such electrophiles are faster than those with perfluoroalkyl halides. To solve this problem, the generation of a perfluoroalkyllithium and its reaction with an electrophile should be separated, though it was difficult or practically impossible to achieve it with a batch macro reactor because perfluoroalkyllithium undergoes β-elimination very rapidly. Thus, we examined the use of a flow microreactor system, because a highly reactive species can be generated and transferred to another location to be used in the next reaction before it decomposes by adjusting the residence time from the millisecond to second time scale. We used a flow microreactor system consisting of three T-shaped micromixers (**M1**, **M2**, and **M3**) and three microtube reactors (**R1**, **R2**, and **R3**) shown in Fig. 2. Tridecafluorohexyl iodide was reacted with MeLi in **M**1 and **R1** to generate tridecafluorohexyllithium, which was subsequently

Table 2 The reactions of perfluoroalkyllithiums with various electrophiles

$CF_3(CF_2)_nCF_2X$	Electrophile	Product	Yield (%)[a]
CF_3CF_2I	PhCHO	C_nF_{2n+1}CH(OH)Ph (n = 2, 3, 4, 5, 6)	84
$CF_3CF_2CF_2I$			80
$CF_3(CF_2)_2CF_2I$			85
$CF_3(CF_2)_3CF_2I$			86
$CF_3(CF_2)_4CF_2I$			80 (74)[b]
$CF_3(CF_2)_4CF_2Br$			71
$CF_3(CF_2)_4CF_2I$	PhC(O)CH$_3$	C_6F_{13}C(OH)(Me)Ph	70
$CF_3(CF_2)_4CF_2I$	PhNCO	PhNHC(O)C$_6F_{13}$	79
$CF_3(CF_2)_4CF_2I$	$\sim\sim$NCO	$\sim\sim$NHC(O)C$_6F_{13}$	86
$CF_3(CF_2)_4CF_2I$	Me$_3$SiOTf	C_6F_{13}SiMe$_3$	30
$CF_3(CF_2)_4CF_2I$	Bu$_3$SnCl	C_6F_{13}SnBu$_3$	2

[a] GC (gas chromatography) yields using an internal standard. [b] Isolated yield.

Fig. 2 A flow microreactor system for perfluoroalkylation by the generation of perfluoroalkyllithiums in the absence of electrophiles. T-shaped micromixers: **M1**(250 μm), **M2**(250 μm), and **M3** (500 μm), microtube reactors: **R1**, **R2**($\phi = 1000$ μm, L = 50 cm), and **R3** ($\phi = 1000$ μm, $L = 50$ cm). Flow rate of a solution of a perfluoroalkyl halide (0.10 M) in Et$_2$O: 9.00 mL min^{-1}; flow rate of a solution of MeLi (0.48 M) in Et$_2$O: 2.25 mL min^{-1}; flow rate of a solution of an electrophile (0.84 M) in Et$_2$O: 1.50 mL min^{-1}; flow rate of methanol: 2.00 mL min^{-1}.

reacted with chlorotributylstannane as an electrophile in **M2** and **R2**. The reaction was carried out varying the temperature (T) and the residence time in **R1** (t^{R1}). As shown in Fig. 3,[16] high yields (> 80%) were obtained with short t^{R1}, such as 0.15 s at −68 °C. The increase in t^{R1} caused a decrease in the yield, presumably because of β-elimination. The present temperature residence time profile is quite effective to unveil the stability of the perfluoroalkyllithium intermediate. In contrast, it is impossible to obtain such information by the *in situ* generation–capture method. It is also noteworthy that the present flow microreactor method has sufficient productivity for laboratory scale synthesis (477 mg min^{-1}).

Under the optimized conditions ($T = -68$ °C, $t^{R1} = 0.15$ s), the reactions of various perfluoroalkyl halides with highly reactive electrophiles, including chlorotributylstannane, trimethylsilyl
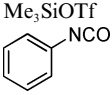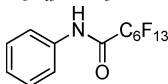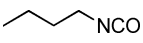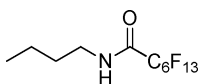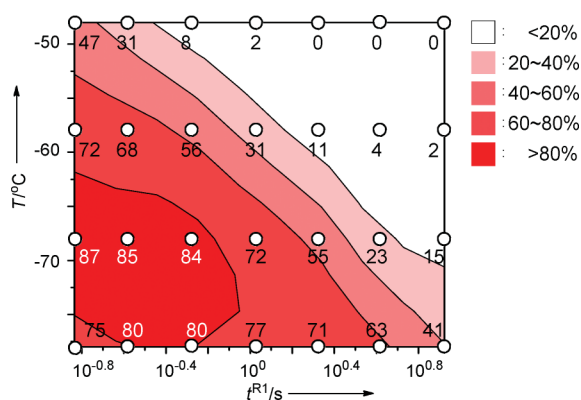
Fig. 3 Effects of the temperature (T) and the residence time (t^{R1}) on the yield of tridecafluorohexylstannane for the reaction of tridecafluorohexyl iodide with MeLi to generate tridecafluorohexyl–lithium followed by the reaction with chlorotributylstannane using the flow microreactor system. Contour plot with scatter overlay of the yields of tridecafluorohexylstannane (%), which are indicated by numbered circles.

triflate and isocyanates, were successfully carried out to obtain the desired products in good yields (Table 3).

Conclusions

In conclusion, we developed an efficient method for perfluoroalkylation using perfluoroalkyllithium intermediates. The *in situ* generation–capture method can be achieved without using an excess of perfluoroalkyl halides at much higher temperatures, such as 0 °C, than those required for batch macro processes. Moreover, the generation of perfluoroalkyllithium in the absence of electrophiles followed by the reaction with subsequently added eletrophiles was also achieved because β-elimination can be avoided by virtue of a short residence time and efficient temperature control in the flow microreactor system. Therefore, the present two methods greatly enhance the synthetic utility of perfluoroalkyllithium intermediates and add a new dimension to the synthesis of organofluorine compounds.

Table 3 The reactions of perfluoroalkyllithiums with various electrophiles

$CF_3(CF_2)_nCF_2X$	Electrophile	Product	Yield (%)[a]
CF_3CF_2I	Bu_3SnCl	$C_nF_{2n+1}SnBu_3$ (n = 2, 3, 4, 5, 6)	98
$CF_3CF_2CF_2I$			81
$CF_3(CF_2)_2CF_2I$			84
$CF_3(CF_2)_3CF_2I$			90
$CF_3(CF_2)_4CF_2I$			87
$CF_3(CF_2)_4CF_2Br$			75
$CF_3(CF_2)_4CF_2I$	Me_3SiOTf	$C_6F_{13}SiMe_3$	82
$CF_3(CF_2)_4CF_2I$	⟨Ph⟩NCO	⟨Ph⟩N(H)C(O)C_6F_{13}	87
$CF_3(CF_2)_4CF_2I$	⟶NCO	⟶N(H)C(O)C_6F_{13}	91

[a] GC yields using an internal standard.

Experimental

General

GC analysis was performed on a SHIMADZU GC-2014 gas chromatograph equipped with a flame ionization detector using a fused silica capillary column (column, CBP1; 0.22 mm × 25 m). ^1H NMR spectra were recorded on Varian MERCURYplus-400 (400 MHz) spectrometer with Me_4Si or $CDCl_3$ as a standard in $CDCl_3$ unless otherwise noted. ^{13}C NMR spectra were recorded on JEOL ECA-600P (150 MHz) spectrometer with $CDCl_3$ as a standard in $CDCl_3$ unless otherwise noted. ^{19}F NMR spectra were recorded on Varian MERCURYplus-400 (377 MHz) spectrometer with trifluorotoluene as a standard in $CDCl_3$ unless otherwise noted. ^{119}Sn NMR spectrum was recorded on JEOL ECA-600P (224 MHz) spectrometer with tetramethyltin as an external standard in $CDCl_3$. EI mass spectra were recorded on a JMS-SX102A spectrometer. APCI mass spectra were recorded on an EXACTIVE spectrometer. The FT-IR spectrum was recorded on a SHIMADZU IRAffinity-1 spectrometer. Gel permeation chromatography (GPC) was carried out on Japan Analytical Industry LC-908 and LC-9201. Diethyl ether was purchased from Kanto Chemical Co., Inc. as a dry solvent and used without further purification. Perfluoroalkyl halide, benzaldehyde, acetophenone, phenyl isocyanate, n-butyl isocyanate, chlorotributylstanane, trimethylsilyl triflate, methanol and MeLi were commercially available. All solutions used for flow reactions were prepared under an argon atmosphere using dry solvents. Stainless steel (SUS304) T-shaped micromixers with inner diameters of 250 and 500 μm were manufactured by Sanko Seiki Co., Inc. Stainless steel (SUS316) microtube reactors with an inner diameter of 1000 μm was purchased from GL Sciences. The micromixer and microtube reactors were connected with stainless steel fittings (GL Sciences, 1/16 OUW). The microflow system was dipped in a cooling bath to control the temperature. Solutions were introduced to the flow microreactor system using syringe pumps, Harvard Model 11, equipped with gastight syringes purchased from SGE.

Typical procedure for the generation of perfluoroalkyllithiums in the presence of electrophiles in the flow microreactor system

A flow microreactor system consisting of two T-shaped micromixers (**M1** and **M2**), two microtube reactors (**R1** and **R2**) and three tube pre-cooling units (**P1** (inner diameter ϕ = 1000 μm, length L = 150 cm), **P2** (ϕ = 1000 μm, L = 50 cm) and **P3** (ϕ = 1000 μm, L = 50 cm)) was used. A mixing solution of $CF_3(CF_2)_nCF_2X$ (0.10 M in Et_2O) and an electrophile (0.12 M in Et_2O) (flow rate: 9.0 mL min^{-1}) and a solution of MeLi (0.42 M in Et_2O) (flow rate: 2.25 mL min^{-1}) were introduced to **M1** (ϕ = 250 μm) by syringe pumps. The resulting solution was passed through **R1** (ϕ = 1000 μm, L = 50 cm) and was mixed with methanol (neat) (flow rate: 3.0 mL min^{-1}) in **M2** (ϕ = 500 μm). The resulting solution was passed through **R2** (ϕ = 1000 μm, L = 50 cm). After a steady state was reached, an aliquot of the product solution was collected for 30 s and was treated with sat. aqueous NH_4Cl solution. The reaction mixture was analyzed by GC using an internal standard.

1-Phenyl-2,2,3,3,3-pentafluoropropan-1-ol. Obtained in 84% yield (GC ^tR 11.6 min). The spectral data were identical to those reported in the literature.[4c]

1-Phenyl-2,2,3,3,4,4,4-heptafluorobutan-1-ol. Obtained in 80% yield (GC ^tR 12.4 min). The spectral data were identical to those reported in the literature.[17]

1-Phenyl-2,2,3,3,4,4,5,5,5-nonafluoropentan-1-ol. Obtained in 85% yield (GC ^tR 13/4 min). The spectral data were identical to those reported in the literature.[17]

1-Phenyl-2,2,3,3,4,4,5,5,6,6,6-undecafluorohexan-1-ol. Obtained in 86% yield (GC ^tR 14.3 min). After extraction, the crude product was purified by column chromatography (hexane/ethyl acetate = 20/1 to 10/1): ^1H NMR (400 MHz, CDCl$_3$) δ 2.51 (d, J = 5.2 Hz, 1H), 5.22 (dt, J = 5.6 Hz, J = 17.6 Hz, 1H), 7.41–7.49 (m, 5H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 72.3 (dd, J = 23.0 Hz, J = 28.0 Hz), 106.2–107.4 (m), 108.0–115.4 (m), 116.2–117.1 (m), 118.3 (t, J = 33.0 Hz), 120.3 (t, J = 33.0 Hz), 128.1, 128.6, 129.7, 134.0; ^{19}F NMR (377 MHz, CDCl$_3$) δ −81.2 (t, J = 10.2 Hz, 3F), −118.0–(−127.6) (m, 8F); HRMS (APCI) m/z calcd for C$_{12}$H$_7$F$_{11}$OCl ([M+Cl]$^-$): 411.0004, found: 441.0014.

1-Phenyl-2,2,3,3,4,4,5,5,6,6,7,7,7-tridecafluoroheptan-1-ol. Obtained in 80% yield (GC ^tR 15.2 min). The spectral data were identical to those reported in the literature.[17]

1-Methyl-1-phenyl-2,2,3,3,4,4,5,5,6,6,7,7,7-tridecafluoroheptan-1-ol. Obtained in 70% yield (GC ^tR 15.5 min). The spectral data were identical to those reported in the literature.[18]

2,2,3,3,4,4,5,5,6,6,7,7,7-Tridecafluoro-N-phenylheptanamide. Obtained in 79% yield (GC ^tR 16.1 min). After extraction, the crude product was purified by column chromatography (hexane/ethyl acetate = 5/1):^1H NMR (400 MHz, CDCl$_3$) δ 7.24–7.28 (m, 1H), 7.38–7.43 (m, 2H), δ 7.55–7.58 (m, 2H), 7.15–7.22 (m, 3H), 7.91 (brs, 1H); ^{13}C NMR (150 MHz, DMSO) δ 105.5–112.7 (m), 113.8 (t, J = 33.0 Hz), 115.7 (t, J = 33.0 Hz), 117.6 (t, J = 33.0 Hz), 119.5 (t, J = 33.0 Hz), 121.3, 125.7, 128.7, 136,3, 155.1 (t, J = 25.8 Hz); ^{19}F NMR (377 MHz, DMSO) δ −82.3 (t, J = 10.2 MHz, 3F), −120.0–(−127.8) (m, 10F); HRMS (EI) m/z calcd for C$_{13}$H$_6$ONF$_{13}$ (M$^+$): 439.0242, found: 270.439.0233.

2,2,3,3,4,4,5,5,6,6,7,7,7-Tridecafluoro-N-n-butylheptanamide. Obtained in 86% yield (GC ^tR 12.5 min). After extraction, the crude product was purified by column chromatography (hexane/ethyl acetate = 10/1 to 5/1): ^1H NMR (400 MHz, CDCl$_3$) δ 0.94 (t, J = 7.2 Hz, 3H), 1.32–1.42 (m, 2H), δ1.53–1.61 (m, 2H), 3.39 (dt, J = 6.4 Hz, J = 6.4 Hz, 3H), 6.30 (brs, 1H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 13.1, 19.8, 30.8, 40.0, 106.2–113.2 (m), 114.4 (t, J = 33.0 Hz), 116.3 (t, J = 33.0 Hz), 118,2 (t, J = 33.0 Hz), 120.1 (t, J = 33.0 Hz), 158.1 (t, J = 25.9 Hz); ^{19}F NMR (377 MHz, CDCl$_3$) δ −81.2 (t, J = 10.2 Hz, 3F), 120.1–(−236.7) (m, 10F); HRMS (APCI) m/z calcd for C$_{11}$H$_{11}$NOF$_{13}$ ([MH]$^+$): 420.0628, found: 420.0618.

Trimethyl(1,1,2,2,3,3,4,4,5,5,6,6,6-tridecafluorohexyl)silane. Obtained in 30% yield (GC ^tR 4.3 min). After extraction, the crude product was purified by GPC: ^1H NMR (400 MHz, CDCl$_3$) δ 0.30 (s, 9H); ^{13}C NMR (150 MHz, CDCl$_3$) δ −4.8, 106.5–107.8 (m), 108.3–114.1 (m), 114.6–115.6 (m), 116.7 (t, J = 33.0 Hz), 118.6 (t, J = 33.0 Hz), 120.5 (t, J = 33.0 Hz), 121.6 (t, J = 44.5 Hz), 123.4 (t, J = 44.5 Hz), 125.2 (t, J = 46.0 Hz); ^{19}F NMR (377 MHz, CDCl$_3$) δ −81.3 (t, J = 10.2 Hz, 3F), −119.4–(−128.9) (m, 10F).

Tri-n-butyl(1,1,2,2,3,3,4,4,5,5,6,6,6-tridecafluorohexyl)-stannane. Obtained in 2% yield (GC ^tR 19.9 min). The spectral data were identical to those reported in the literature.[19]

Typical procedure for the generation of perfluoroalkyllithiums in the absence of electrophiles in the flow microreactor system

A flow microreactor system consisting of three T-shaped micromixers (**M1**, **M2** and **M3**), three microtube reactors (**R1**, **R2** and **R3**), and four tube pre-cooling units (**P1**(inner diameter ϕ = 1000 μm, length L = 150 cm), **P2** (ϕ = 1000 μm, L = 50 cm) and **P3** (ϕ = 1000 μm, L = 50 cm), **P4** (ϕ = 1000 μm, L = 50 cm)) was used. A solution of perfluoroalkyl halide (0.10 M in Et$_2$O) (flow rate: 9.0 mL min^{-1}) and a solution of MeLi (0.48 M in Et$_2$O) (flow rate: 2.25 mL min^{-1}) were introduced to **M1** (ϕ = 250 μm) by syringe pumps. The resulting solution was passed through **R**1 and was mixed with a solution of an electrophile (0.84 M in Et$_2$O) (flow rate: 1.5 mL min^{-1}) in **M2** (ϕ = 250 μm). The resulting solution was passed through **R2** (ϕ = 1000 μm, L = 50 cm) and was quenched by mixing with methanol (flow rate: 2.0 mL min^{-1}) in **M3** (ϕ = 500 μm). The resulting solution was passed through **R3** (ϕ = 1000 μm, L = 50 cm). After a steady state was reached, an aliquot of the product solution was collected for 30 s and was treated with sat. aqueous NaHCO$_3$ solution. The reaction mixture was analyzed by GC using an internal standard.

Tri-n-butyl(1,1,2,2,2-pentafluroroethyl)stannane. Obtained in 98% yield (GC ^tR 18.0 min). The spectral data were identical to those commercially available sample.

Tri-n-butyl(1,1,2,2,3,3,3-heptafluorooopropyl)stannane. Obtained in 70% yield (GC ^tR 18.2 min). The spectral data were identical to those reported in the literature.[20]

Tri-n-butyl(1,1,2,2,3,3,4,4,4-nonafluorobutyl)stannane. Obtained in 84% yield (GC ^tR 18.7 min). The spectral data were identical to those reported in the literature.[20]

Tri-n-butyl(1,1,2,2,3,3,4,4,5,5,5-undecafluoropentyl)stannane. Obtained in 90% yield (GC ^tR 19.2 min). After extraction, the crude product was purified by GPC: ^1H NMR (400 MHz, CDCl$_3$) δ 0.30 (s, 9H), 0.92 (t, J = 7.4 Hz, 3H), 1.10–1.39 (m, 4H), 1.46–1.67 (m, 2H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 10.7, 13.4, 27.3, 28.5, 106.4–107.6 (m), 108.2–115.1 (m), 116.8 (t, J = 33.0 Hz), 118.7 (t, J = 33.0 Hz), 120.6 (t, J = 33.0 Hz), 127.7–133.2 (m); ^{19}F NMR (377 MHz, CDCl$_3$) δ −81.3 (t, J = 10.2 Hz, 3F), −117.8–(−126.8) (m, 8F); ^{119}Sn NMR (224 MHz, CDCl$_3$) δ 0.51 (t, J = 191 Hz); HRMS (EI) m/z calcd for C$_{13}$H$_{18}$F$_{11}$Sn ([M−Bu]$^+$): 503.0255, found: 503.0254.

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