Nucleophilic introduction of fluorinated alkyl groups into aldehydes and ketones using the corresponding alkyl halide with samarium(II) iodide

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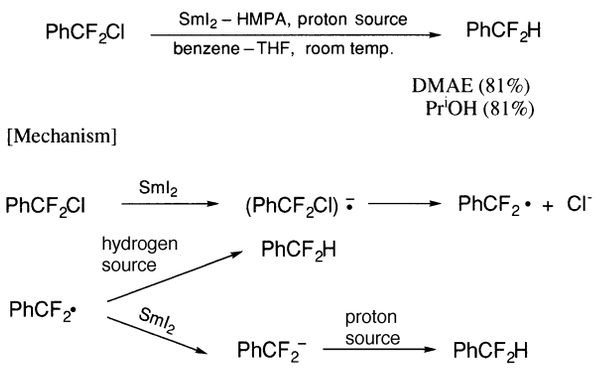
Fluorinated alkyl groups such as $PhCF_2$, C_6F_{13}, CF_3CCl_2 and CF_2CO_2Et are nucleophilically introduced into an aldehyde or ketone using fluorinated alkyl halides with SmI_2; the reaction proceeds effectively at room temperature to give the corresponding alcohol. Furthermore, the synthesis of $PhCF_2SiMe_3$, $C_6F_{13}SiMe_3$ and $C_6F_{13}SiMe_2Pr^i$ is achieved by reaction of the halide with SmI_2 in the presence of the silyl chloride; the resultant fluoroalkylated silyl compounds are used as reagents for nucleophilic fluoroalkylation. 2-Chloro-3,3,3-trifluoropropene derivatives are also prepared selectively by the reaction of CF_3CCl_3 with an excess of SmI_2 in the presence of an aldehyde and Pr^iOH.

Nucleophilic introduction of a fluorinated alkyl group into organic molecules is an important route for the synthesis of organofluorine compounds. Although organometallic reagents have recently played important and versatile roles for nucleophilic alkylation, their applicability to fluorine analogues is very limited.[1] This is due to the thermal instability and low nucleophilicity of fluoroalkyl metallic reagents. Fluoroalkyllithium and Grignard reagents are very unstable, undergoing α- or β-elimination of the fluoride ion whilst, in contrast, fluoroalkylzinc, -copper and -mercury reagents are stable, but have low nucleophilicity. Thus, development of a novel method for the nucleophilic introduction of a fluorinated alkyl group into organic molecules is of importance. In continuing our efforts to develop novel synthetic methods for organofluorine compounds, we have been investigating nucleophilic fluoroalkylation using a fluoroalkyl halide with samarium(II) iodide (SmI_2), and the results are reported here.

We investigated the introduction of CF_2Cl into aromatic rings and successive conversion of the chlorine into other functional groups.[2] In the course of our study, we found that SmI_2 was a very useful reagent for the one-electron reductive cleavage of the C–Cl bond of $PhCF_2Cl$, leading to the $PhCF_2$ radical and chloride ion; these results have been reported in our previous papers.[3] Now we have found that the $PhCF_2$ radical, thus formed, is further reduced to the $PhCF_2$ anion with SmI_2. To a solution of $PhCF_2Cl$ in benzene in the presence of HMPA and a proton source such as 2-dimethylaminoethanol (DMAE) or propan-2-ol (Pr^iOH), a THF solution of SmI_2 was added at room temperature. The reaction was complete within 5 min, and then work-up gave $PhCF_2H$ as the sole product (Scheme 1). In the presence of CH_3OD (MeOD), $PhCF_2D$ was obtained almost exclusively; this means that the reduction proceeds predominantly along an ionic path *via* the $PhCF_2$ anionic species (Scheme 1: mechanism).

In the absence of HMPA, the reaction was very slow, requiring more than 3 h for the disappearance of the colour of SmI_2. The reduction potential of the C–Cl bond in $PhCF_2Cl$ is relatively high,[4] and SmI_2 alone is not enough for the reduction [$E^\circ_{aq}(Sm^{+2}/Sm^{+3}) = -1.55$ V].[5] However, the reduction of $PhCF_2Cl$ could be achieved by the addition of HMPA; employing HMPA as an additive to SmI_2 is known to enhance its reductive ability.[6]

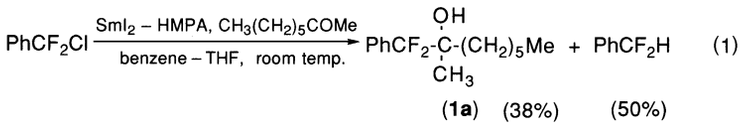
Thus, the reaction of $PhCF_2Cl$ with SmI_2 in the presence of an electrophile such as octan-2-one, acetophenone, benzaldehyde or trimethylsilyl chloride (TMSCl) was investigated;

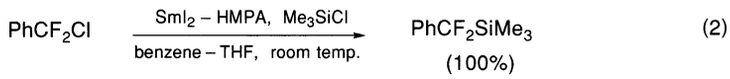


Scheme 1

$PhCF_2Cl$ and the electrophile in benzene were added to a solution of SmI_2 in THF in the presence of HMPA. In the reaction with octan-2-one, the alcohol **1a** and $PhCF_2H$ were obtained in 38 and 50% yields, respectively [Scheme 2, eqn. (1)]. Probably, the $PhCF_2$ anionic species attacked both the carbonyl carbon and the α-hydrogen of octan-2-one to give the alcohol **1a** and $PhCF_2H$, respectively. The anionic species was also very reactive towards TMSCl, giving $PhCF_2SiMe_3$ almost quantitatively [Scheme 2, eqn. (2)]. The applicability of this Barbier type reaction to aldehydes or ketones was, however, very limited; SmI_2–HMPA reacted with benzaldehyde or acetophenone much faster than with $PhCF_2Cl$, and the desired alcohol was not obtained. Therefore a two-step procedure was examined; $PhCF_2Cl$ was added to a solution of SmI_2–HMPA in THF under nitrogen, and then octan-2-one was added stepwise to the resulting solution. In the two-step procedure, neither the desired alcohol nor $PhCF_2H$ was obtained. Probably, the reactive $PhCF_2$ anion equivalent was formed initially by the reaction of $PhCF_2Cl$ with SmI_2–HMPA but immediately converted to a more stable species, which no longer reacted with these electrophiles. Unfortunately, the nature of the reactive anionic intermediate is not yet clear.

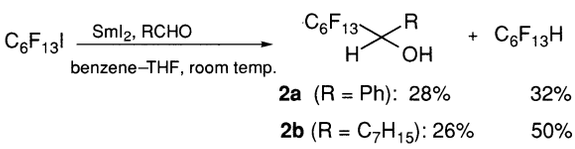
These results prompted us to investigate the reaction of a perfluoroalkyl halide with SmI_2 for comparison with that of $PhCF_2Cl$. A solution of $C_6F_{13}I$ and an aldehyde or ketone (10 equiv. to $C_6F_{13}I$) in benzene was added to a solution of SmI_2 in THF. The reaction of $C_6F_{13}I$ proceeded at room temperature without HMPA, and was complete within 1 min. After treat-





Scheme 2

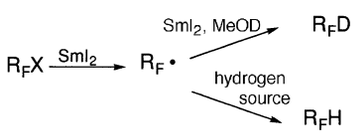
ment with MeOH, yields of the products were determined by ^{19}F NMR spectroscopy based on $C_6F_{13}I$ (Scheme 3). The yields



Scheme 3

of the adducts of C_6F_{13} to aldehydes were not good and a considerable amount of the reduced product ($C_6F_{13}H$) was obtained (Scheme 3). Thus reaction with the ketone did not occur.

The production of $C_6F_{13}H$ in the reaction with PhCHO is likely to be due to hydrogen abstraction from THF by the initially formed C_6F_{13} radical. In order to confirm this, we examined the reaction with MeOD (Scheme 4). The reaction of



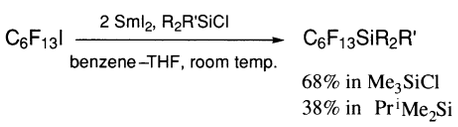
$R_F D / R_F H$ in THF = 68 : 32 ($R_F = C_6F_{13}$), 100 : 0 ($R_F = PhCF_2$)

$R_F D / R_F H$ in CH_3CN = 84 : 16 ($R_F = C_6F_{13}$)

Scheme 4

$C_6F_{13}I$ with SmI_2 in the presence of MeOD gave both $C_6F_{13}D$ and $C_6F_{13}H$ in the ratio of 68:32. This means that 32% of the C_6F_{13} radical abstracted hydrogen mainly from THF and about 68% of the C_6F_{13} radical was further reduced with SmI_2 to a C_6F_{13} anionic species. The result is much different from that observed in $PhCF_2Cl$; $PhCF_2D$ was obtained almost exclusively from $PhCF_2Cl$. Probably this is due to the higher reactivity of the C_6F_{13} radical for hydrogen abstraction compared to the $PhCF_2$ radical. When CH_3CN was used as a solvent, the ionic path in C_6F_{13} to give $C_6F_{13}D$ was increased to 84%. The yield of $C_6F_{13}H$ on reaction with $C_7H_{15}CHO$ was higher than that with PhCHO (Scheme 3). This suggests that during reaction with $C_7H_{15}CHO$, proton abstraction from the α-hydrogen of the aldehyde by the anionic species occurs in addition to hydrogen abstraction by the radical.

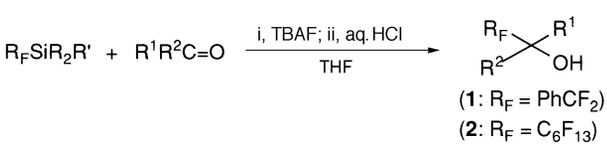
The C_6F_{13} anionic species reacted with trimethylsilyl chloride efficiently, and a silylated product was obtained in 68% yield (Scheme 5); $C_6F_{13}SiMe_3$ was not isolated in a pure form due



Scheme 5

to its high volatility and the yield was determined by ^{19}F NMR spectroscopy based on $C_6F_{13}I$ using $PhCF_3$ as an internal standard. Conveniently, pure $C_6F_{13}SiMe_2Pr^i$ was obtained by reaction with Pr^iMe_2SiCl and was characterized by ^1H, ^{13}C and ^{19}F NMR spectroscopy (see Experimental section).

Fluoroalkylsilane derivatives have recently been recognized as convenient reagents for the introduction of fluoroalkyl groups into carbonyl compounds, and facile methods for their preparation have been investigated.[7] The method using SmI_2 described here is expected to be novel and practically useful for the preparation of $PhCF_2SiMe_3$, $C_6F_{13}SiMe_3$ and $C_6F_{13}SiMe_2Pr^i$. The reactivity of CF_3SiMe_3 has been extensively investigated,[7] but little is known about the reactions of $PhCF_2SiMe_3$ and $C_6F_{13}SiMe_3$. Thus, we investigated the reaction of these silyl compounds with aldehydes and a ketone. The reaction was carried out in THF in the presence of a catalytic amount of tetrabutylammonium fluoride (TBAF) to give the alcohols **1** and **2**.



$PhCF_2SiMe_3$ was treated with the aldehydes to give the alcohols **1b** and **1c** in good yields (Table 1). However, reactivity of the carbonyl carbon of the ketone was low (Table 1), and a considerable amount of $PhCF_2H$ was produced by reaction with the α-hydrogen of the ketone. As mentioned previously, the corresponding alcohols were not obtained from reaction of $PhCF_2Cl$ with SmI_2–HMPA in the presence of an aldehyde, because the aldehyde was reduced much faster than $PhCF_2Cl$. Therefore, $PhCF_2SiMe_3$ is important as an efficient reagent for the introduction of the $PhCF_2$ unit into the aldehyde. Similarly, $C_6F_{13}SiMe_3$ and $C_6F_{13}SiMe_2Pr^i$ were treated with aldehydes to give the corresponding alcohol in moderate to good yields (Table 1), but did not react with the ketone.

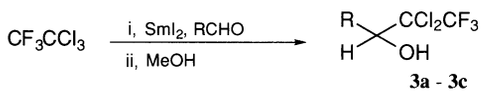
The synthetic utility of SmI_2 for the nucleophilic introduction of fluorinated alkyl groups such as CF_3CCl_2 and CF_2CO_2Et was further investigated. The 1,1-dichloro-2,2,2-trifluoromethyl (CF_3CCl_2) unit has recently been the focus of attention because of its versatility in the synthesis of organofluorine compounds with potential importance in industry and because the reactions of CF_3CCl_3 with Zn[8] and $PbBr_2$–Al,[9] upon electroreduction[10] are known to be useful for introduction of the group into electrophiles. Thus, the reaction of CF_3CCl_3 with SmI_2 in the presence of an electrophile was investigated. A solution of CF_3CCl_3 and an aldehyde (2 equiv. to CF_3CCl_3) in benzene was added to a solution of SmI_2 (2.4 equiv. to CF_3CCl_3) under nitrogen. The reaction was completed within 10 min and after treatment of the mixture with MeOH, the product yields were determined by ^{19}F NMR spectroscopy using $PhCF_3$ as an internal standard. The alcohols **3** were obtained in moderate yields (Scheme 6).

Further reduction of the Cl in **3** with SmI_2 is expected; on reaction of **3** with SmI_2 in the presence of Pr^iOH, the olefins **4** were obtained selectively; other possible olefins **5** were absent (Scheme 7). The presence of Pr^iOH was essential for the selective formation of **4**. Both **4b** and **5b** were obtained in the ratio of 19:81 by the reaction of **3b** with SmI_2 in the absence of Pr^iOH.

Table 1 Reaction of R_FSiR_2R' with aldehydes and a ketone

$R_FSiR^1R^2R^3$	Electrophile	Product	Yield (%)[a]
$PhCF_2SiMe_3$	$Me(CH_2)_5(CO)Me$	**1a**	12
$PhCF_2SiMe_3$	PhCHO	**1b**	70
$PhCF_2SiMe_3$	$Me(CH_2)_6CHO$	**1c**	58
$C_6F_{13}SiMe_3$	PhCHO	**2a**	47
$C_6F_{13}SiMe_3$	$Me(CH_2)_6CHO$	**2b**	41
$C_6F_{13}SiMe_2Pr^i$	PhCHO	**2a**	55
$C_6F_{13}SiMe_2Pr^i$	$Me(CH_2)_6CHO$	**2b**	63

[a] Determined by ^{19}F NMR spectroscopy based on R_FSiR_2R'.



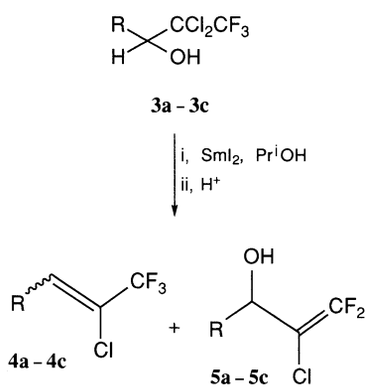
3a - 3c

RCHO	Yield (%)[a]	
a $PhCH_2CH_2CHO$	51	
b Ph(Me)CHCHO	52	(88 : 12)[b]
c $Me(CH_2)_6CHO$	46	

[a] Determined by ^{19}F NMR spectroscopy based on CF_3CCl_3.

[b] Ratio of the isomers.

Scheme 6



Yield of **4**

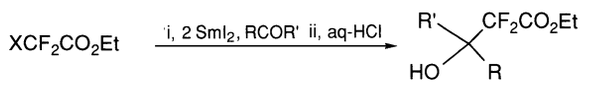
a 65% ($Z : E$ = 88 : 12)
b 81% ($Z : E$ = 96 : 4)
c 92% ($Z : E$ = 94 : 6)

Scheme 7

Application of SmI_2 to the Reformatsky-type reaction was also successful, and a part of this work has been reported as a preliminary communication.[11] The Reformatsky-type reaction is known to be one of the most useful methods for the construction of α,α-difluorinated compounds from XCF_2CO_2R (X = I, Br or Cl), Zn being used to induce the reaction.[12] After the initial report of Hallinan and Fried,[13] several modified methods have been investigated mainly concerned with activation of the Zn to realize the reaction efficiently by the use of additives[14] or sonicating conditions.[15] We have found that SmI_2, as an alternative reagent to Zn, induced the reactions of XCF_2CO_2Et (X = Cl and Br) with aldehydes and ketones effectively at room temperature to give 2,2-difluoro-3-hydroxy esters **6**. Unfortunately, the reaction of $BrCF_2CO_2Et$ with an ester (RCO_2Et), amide (RNHCOMe) or imine ($R^1CH{=}NR^2$) was not realized by SmI_2.

When a solution of XCF_2CO_2Et (X = Cl or Br) and an aldehyde or ketone in THF was added to a solution of SmI_2 in THF at room temperature under nitrogen, the colour of the solution turned from purple to yellow at once, indicating the end of the reaction. Reasonable yields were obtained for both aldehydes and ketones, other than benzaldehyde (see Table 2). Benzaldehyde itself reacted with SmI_2 and prevented the effective reaction of $BrCF_2CO_2Et$ with SmI_2. The SmI_2-induced reactions were complete within 1 min at room temperature for both $BrCF_2CO_2Et$ and $ClCF_2CO_2Et$. Zn-induced reactions of $ClCF_2CO_2Et$ failed under the reaction conditions which were normally effective with $BrCF_2CO_2Et$ (reflux in THF for 30 min), and required high temperature (70 °C), longer reaction time (20 h) and a solvent of higher polarity such as DMF.[16] It is, therefore, of particular importance to note that the reaction of inexpensive $ClCF_2CO_2Et$ with SmI_2 was complete at room temperature within 1 min in THF, although electrochemically induced intermolecular coupling of $ClCF_2CO_2Me$ with an aldehyde has been reported to take place effectively in DMF.[10]

Table 2 Reaction of XCF_2CO_2Et with SmI_2 in the presence of aldehydes or ketones



X = Cl and Br

6

RCOR′	X	Product	Yield (%)[a]
$Me(CH_2)_6CHO$	Br	**6a**	67 (67)
	Cl		74
$Ph(CH_2)_2CHO$	Br	**6b**	87 (79)
Ph(Me)CHCHO	Br	**6c**	93[b] (90)[c]
	Cl		91[b]
$MeCO(CH_2)_5Me$	Br	**6d**	85 (71)
	Cl		94
PhCOMe	Br	**6e**	56 (58)
	Cl		29
Cyclohexanone	Br	**6f**	99 (91)
	Cl		89
PhCOPh	Br	**6g**	46 (47)
4-*tert*-Butyl-cyclohexanone	Br	**6h**	91[b] (72)[c]
	Cl		91[b]
PhCHO	Br	**6i**	27

[a] The yields were determined by ^{19}F NMR spectroscopy using $PhCF_3$ as an internal standard based on XCF_2CO_2Et; XCF_2CO_2Et (1.0 mmol) and carbonyl compound (2.0 mmol) were used for the reaction. Isolated yields based on carbonyl compound are shown in parenthesis; the reactions were performed using $BrCF_2CO_2Et$ (1.0 mmol) and carbonyl compound (0.9 mmol) (see Experimental section). [b] Ratios of the isomers determined by ^{19}F NMR spectroscopy: in **6c** 42:58 (X = Br), 40:60 (X = Cl) and in **6h** 51:49 (X = Br), 51:49 (X = Cl). [c] Total yield of the two isomers.

In summary, although SmI_2 has recently been recognized to be an effective one-electron reducing reagent, and is used in a variety of organic syntheses,[5] its utility in organofluorine chemistry for the formation of reactive species from fluorinated alkyl halides has been less developed.[17] In our study, SmI_2 has been shown, when used with various fluorinated alkyl halides, to induce the nucleophilic introduction of the corresponding alkyl groups. Since SmI_2 is readily available and easy to handle, the procedure described here is expected to be convenient and practically useful for the synthesis of organofluorine compounds.

Experimental

Melting points were measured with a Yanaco MP-500D melting point apparatus, and are uncorrected. ^1H, ^{13}C and ^{19}F NMR spectra were taken with a JEOL JNM EX400 (400 MHz ^1H, 100 MHz ^{13}C and 376 MHz ^{19}F NMR) spectrometer. Fluorine chemical shifts are given in ppm from external CF_3CO_2H. *J* Values are recorded in Hz. Mass spectra were obtained with a JEOL JMS AX-505W spectrometer with a JEOL JMA 5000 mass data system using an electron-impact (EI) ionization technique at 70 eV. Gel-permeation chrom-

atography (GPC) was performed by means of a JAI model LC-908 liquid chromatograph equipped with two JAIGEL-1H columns (20 × 600 mm) with chloroform as eluent.

Materials

Samarium(II) iodide (SmI_2) was used as a THF solution (0.1 mol l^{-1}); it was synthesized from samarium powder by reaction with I_2 in THF under nitrogen according to the literature,[18] or obtained from Aldrich Co. Ltd., as a THF solution (0.1 mol l^{-1}). Samarium ingots (99.9% purity) were obtained from Soekawa Chemicals Co. Ltd., and were powdered with a rasp. The concentration of SmI_2 was determined by iodometry prior to use as described in the literature.[18] $PhCF_2Cl$ was prepared by the reaction of benzene with bis(chlorodifluoroacetyl) peroxide as described in our previous paper.[2] Due to the high volatility of $PhCF_2Cl$, complete separation from benzene was difficult. Therefore, a benzene solution of $PhCF_2Cl$ (0.15–0.20 mol l^{-1}) was prepared and used for the reactions described; the concentration of the solution was determined by ^{19}F NMR spectroscopy using $PhCF_3$ as an internal standard. Perfluorohexyl iodide ($C_6F_{13}I$) was obtained from F-Tech. Inc. and distilled prior to use. 1,1,1-Trichloro-2,2,2-trifluoroethane (CF_3CCl_3) and ethyl bromodifluoroacetate ($BrCF_2CO_2Et$) were available from Tokyo Kasei Kogyo Co. Ltd., and purified by distillation prior to use. Tetrabutylammonium fluoride (1 mol l^{-1} in THF) was also available from Tokyo Kasei Kogyo Co. Ltd., and dried over molecular sieves (MS-4A) prior to use. Ether refers to diethyl ether.

Reaction of $PhCF_2Cl$ with SmI_2 in the presence of an electrophile

To a solution of SmI_2 (2.5 mmol) in THF was added $PhCF_2Cl$ (1.0 mmol), octan-2-one (10 mmol) in benzene (5 ml) and then HMPA (7.5 mmol) under nitrogen at room temperature with stirring. After 1 min, aq. HCl (1 mol dm^3) was added to the mixture and the organic products were extracted with ether (3 × 20 ml). The combined extracts were washed with water, dried ($MgSO_4$) and evaporated. Purification of the residue with GPC gave the corresponding alcohol **1a**.

1-Phenyl-1,1-difluoro-2-methyloctan-2-ol **1a**: colourless oil (Found: C, 70.21; H, 8.92. $C_{15}H_{22}OF_2$ requires C, 70.28; H, 8.65%); δ_H(400 MHz, $CDCl_3$) 7.48–7.55 (m, 2 H), 7.38–7.45 (m, 3 H), 1.26 (s, 3 H), 1.16–1.59 (m, 10 H) and 0.87 (t, 3 H, *J* 6.84); δ_C(100 MHz, $CDCl_3$) 134.3 (t, *J* 26.7), 129.7, 127.8, 126.9, 123.1 (t, *J* 251), 75.7 (t, *J* 28.5), 35.5, 31.8, 29.8, 22.8, 22.6, 20.3 and 14.0; δ_F(376 MHz, $CDCl_3$ from ex. CF_2CO_2H) −32.7 and −33.5 (ABq, *J* 247); *m*/*z* 256 (M^+), 129 and 127.

Similarly, (phenyldifluoromethyl)trimethylsilane ($PhCF_2SiMe_3$) was obtained: δ_H(400 MHz, $CDCl_3$) 7.28–7.45 (m, 5 H) and 0.142 (s, 9 H); δ_C(100 MHz, $CDCl_3$) 138.2 (t), 128.8, 128.2, 124.6 and −4.86; δ_F(376 MHz, $CDCl_3$ from ex. CF_3CO_2H) −37.0 (s, 2 F); *m*/*z* 200 (M^+), 127, 108, 77 and 73 (Found: M^+, 200.0827. $C_{10}H_{14}F_2Si$ requires *M*, 200.0832).

Reaction of $PhCF_2SiMe_3$ with carbonyl compounds

A solution of $PhCF_2SiMe_3$ (1.0 mmol) and benzaldehyde (10 mmol) in THF (2 ml) was dried over molecular sieves (MS-4A), after which tetrabutylammonium fluoride (TBAF; 0.1 mmol) was added to it at room temperature under nitrogen. The resulting solution was stirred at room temperature for 1 h after which aq. HCl (1 mol l^{-1}; 20 ml) was added and stirring continued at room temperature for 1 h. The mixture was then extracted with ether (3 × 20 ml) and the combined extracts were washed with water, dried ($MgSO_4$) and evaporated. Purification of the residue with GPC gave the corresponding alcohol **1b**.

1,2-Diphenyl-2,2-difluoroethanol **1b**: colourless crystals from hexane, mp 90.5–91.0 °C (Found: C, 71.80; H, 5.29. $C_{14}H_{12}OF_2$ requires C, 71.79; H, 5.16%); δ_H(400 MHz, $CDCl_3$) 7.16–7.39 (m, 10 H), 5.04 (t, 1 H, J_{HF} 9.2) and 2.99 (s, 1 H); δ_C(100 MHz, $CDCl_3$) 135.8, 133.7 (t, *J* 25.8), 129.9, 128.5, 127.82, 127.77, 127.71, 126.2 (t, *J* 5.5), 121.1 (t, *J* 248) and 76.7 (t, *J* 30.3); δ_F(376 MHz, $CDCl_3$ from ex. CF_3CO_2H) −28.95 and −32.82 (ABq, J_{FF} 252, d, J_{HF} 9.2); *m*/*z* 234 (M^+), 127 and 107.

Similarly, 1-(phenyldifluoromethyl)nonanol **1c** was obtained as colourless crystals from hexane, mp 48.7–49.5 °C (Found: C, 70.56; H, 9.01. $C_{15}H_{22}OF_2$ requires C, 70.28; H, 8.65%); δ_H(400 MHz, $CDCl_3$) 7.49–7.51 (m, 2 H), 7.41–7.44 (m, 3 H), 3.90–3.99 (m, 1 H), 1.99 (s, 1 H), 1.25–1.61 (m, 12 H) and 0.86 (t, 3 H, *J* 6.84); δ_C(100 MHz, $CDCl_3$) 134.4 (t, *J* 25.7), 130.0, 128.3, 125.9, 121.7 (t, *J* 246), 74.4 (t, *J* 30.4), 31.7, 30.0, 29.3, 29.1, 25.5, 22.6 and 14.0; δ_F(376 MHz, $CDCl_3$ from ex. CF_3CO_2H) −31.47 and −32.57 (ABq, *J* 249, d, J_{HF} 9.8); *m*/*z* 256 (M^+), 129 and 127.

Reaction of $C_6F_{13}SiMe_3$ with carbonyl compounds

$C_6F_{13}SiMe_3$ was obtained as a THF solution by reaction of $C_6F_{13}I$ with SmI_2 in the presence of Me_3SiCl. To a solution of SmI_2 (2.2 mmol) in THF was added $C_6F_{13}I$ (1.0 mmol) and Me_3SiCl (10 mmol) in benzene (2 ml) under nitrogen at room temperature with stirring. The characteristic colour of SmI_2 disappeared within 1 min. $C_6F_{13}SiMe_3$ and THF were distilled from the reaction mixture, and the concentration of the former was determined by ^{19}F NMR spectroscopy using $PhCF_3$ as an internal standard. The solution of $C_6F_{13}SiMe_3$ in THF was used in the following reactions without further purification. A solution of $C_6F_{13}SiMe_3$ (1.0 mmol) and benzaldehyde (10 mmol) in THF (2 ml) was dried over MS-4A for 1 h, after which TBAF was added to it. The resulting solution was stirred at room temperature under nitrogen for 1 h after which aq. HCl (1 mol l^{-1}; 20 ml) was added and stirring continued for 1 h at room temperature. After this the mixture was extracted with ether (3 × 20 ml) and the combined extracts were washed with water, dried ($MgSO_4$) and evaporated. Purification of the residue with GPC gave the corresponding alcohol **2a**[19] as a colourless oil. Similarly, **2b**[19] was obtained.

Synthesis of $C_6F_{13}SiMe_2Pr^i$

To a solution of SmI_2 (2.2 mmol) in THF was added $C_6F_{13}I$ (1.0 mmol) and Pr^iMe_2SiCl (10 mmol) in benzene (2 ml) under nitrogen at room temperature with stirring. After 1 min, aq. HCl (1 mol dm^3) was added to the mixture which was then extracted with ether (3 × 20 ml). The combined extracts were washed with water, dried ($MgSO_4$) and evaporated. Purification of the residue with GPC gave $C_6F_{13}SiMe_2Pr^i$; δ_H(400 MHz, $CDCl_3$) 1.12–1.21 (m, 1 H), 1.06 (d, 6 H, *J* 6.8) and 0.25 (s, 6 H); δ_C(100 MHz, $CDCl_3$) 17.0, 11.3 and −7.9; δ_F(376 MHz, $CDCl_3$ from ex. CF_3CO_2H) −5.5 (t, 3 F, *J* 9.2), −43.3 (2 F), −46.6 (2 F), −47.5 (2 F), −50.0 (2 F) and −50.8 (2 F).

Reaction of $C_6F_{13}SiMe_2Pr^i$ with carbonyl compounds

$C_6F_{13}SiMe_2Pr^i$ (1.0 mmol) and benzaldehyde (10 mmol) in THF (2 ml) were dried over MS-4A for 1 h, after which TBAF was added to the mixture. This was then stirred at room temperature under nitrogen for 1 h. Aq. HCl (1 mol l^{-1}; 20 ml) was then added to the solution which was stirred at room temperature for a further 1 h. Finally, the mixture was extracted with ether (3 × 20 ml) and the combined extracts were washed with water, dried ($MgSO_4$) and evaporated. Purification of the residue with GPC gave the corresponding alcohol **2a** as a colourless oil. Similarly, the reaction with $CH_3(CH_2)_6CHO$ was performed to give **2b**.

Reaction of CF_3CCl_3 with SmI_2 in the presence of a carbonyl compound

A solution of CF_3CCl_3 (0.05 mmol) and aldehyde (0.10 mmol) in benzene was added to a solution of SmI_2 (0.12 mmol) in THF under nitrogen at room temperature with stirring. The resulting solution was allowed to react at room temperature for 7 min after which it was treated with MeOH. Yields of the products were determined by ^{19}F NMR spectroscopy using $PhCF_3$ as an internal standard. Product **3** and the recovered

aldehyde could not be completely separated so the following method was employed for the isolation of **3**.

A solution of CF_3CCl_3 (1.26 mmol) and 2-phenylpropionaldehyde (1.1 mmol) in benzene (2 ml) was added to a stirred solution of SmI_2 (2.7 mmol) in THF, and stirring continued for 10 min. After treatment with aq. HCl (1 mol l^{-1}; 20 ml) the mixture was extracted with hexane (3 × 20 ml) and the combined extracts were washed with water, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography with silica gel (Daisogel IR-60) using CH_2Cl_2 as eluent. The corresponding alcohol **3a** (135 mg) was obtained in 43% isolated yield based on the aldehyde; δ_H(400 MHz, $CDCl_3$) 7.20–7.31 (m, 5 H, Ph), 4.06 (t, 1 H, *J* 6.8), 2.92–2.97 (m, 1 H), 2.70–2.76 (m, 1 H), 2.34 (s, 1 H, OH), 2.28–2.36 (m, 1 H) and 1.90–2.01 (m, 1 H); δ_C(100 MHz, $CDCl_3$) 140.5, 128.6, 128.4, 126.3, 122.1 (q, *J* 285), 88.3 (q, *J* 31.3), 75.1, 33.0 and 31.6; δ_F(376 MHz, $CDCl_3$ from ex. CF_3CO_2H) 1.41 (s, 3 F); *m*/*z* 288 (M + 2), 286 (M^+), 233, 214, 177 and 69 (Found: M^+, 286.0118, $C_{11}H_{11}F_3OCl_2$ requires *M*, 286.0139).

Similarly, **3b** was obtained in 43% isolated yield, and characterized by comparison with the reported spectral data.[8]

Alcohol **3c** was also obtained in 26% isolated yield; δ_H(400 MHz, $CDCl_3$), 4.08 (t, 1 H, *J* 8.1), 2.17 (br s, 1 H), 1.94–2.02 (m, 1 H), 1.59–1.64 (m, 2 H), 1.29–1.42 (m, 9 H) and 0.89 (t, 3 H, *J* 6.8); δ_C(100 MHz, $CDCl_3$) 122.2 (q, *J* 284), 88.4 (q, *J* 31.2), 75.9, 31.7, 31.6, 29.2, 29.1, 25.7, 22.6 and 14.0; δ_F[376 MHz, $CDCl_3$–THF (1:1) from ex. CF_3CO_2H] 1.3 (s, 3 F); *m*/*z* 282 (M + 2), 280 (M^+), 262, 226 and 69 (Found: M^+, 280.0607. $C_{10}H_{17}F_3OCl_2$ requires *M*, 280.0608).

Selective preparation of the olefin 4

After CF_3CCl_3 (1.0 mmol) had reacted with 2-phenylpropionaldehyde (0.9 mmol) in the presence of a slight excess of SmI_2 (2.2 mmol), additional SmI_2 (2.0 mmol) was added to the reaction mixture with Pr^iOH. The resulting mixture was stirred for a further 1 h at room temperature under nitrogen, after which it was treated with aq. HCl (1 mol l^{-1}; 40 ml) and extracted with hexane (3 × 20 ml). The combined extracts were washed with water, dried ($MgSO_4$) and evaporated. The resulting residue was purified by column chromatography (Daisogel IR-60) using hexane as eluent to give the corresponding *Z*-olefin, *Z*-**4a**, (38 mg; total yield from the aldehyde: 18%). Similarly, *Z*-**4b** and *Z*-**4c** were obtained in 32 and 35% yields, respectively. New compounds **4a** and **4c** were characterized from their spectral data.

Compound **4a**: δ_H(400 MHz, $CDCl_3$) 7.17–7.32 (m, 5 H, Ph), 6.48 (t, 1 H, *J* 7.1), 2.77 (t, 2 H, *J* 7.1) and 2.65 (q, 2 H, *J* 7.1); δ_C(100 MHz, $CDCl_3$) 140.1, 133.3, 128.6, 128.3, 126.4, 121.9 (q, *J* 36.7), 120.3 (q, *J* 272), 38.6 and 29.7; δ_F(376 MHz, $CDCl_3$ from ex. CF_3CO_2H) 6.3 (s, 3 F); *m*/*z* 236 (M + 2), 234 (M^+), 199 and 91 (Found: M^+, 234.0429. $C_{11}H_{10}F_3Cl$ requires *M*, 234.0423).

Compound **4c**: δ_H(400 MHz, $CDCl_3$) 6.46 (t, 1 H, *J* 7.33), 2.26–2.32 (m, 2 H), 1.45–1.48 (m, 2 H), 1.29–1.31 (m, 8 H) and 0.89 (t, 3 H, *J* 7.08); δ_C(100 MHz, $CDCl_3$) 134.7, 120.5 (q, *J* 272), 121.2 (q, *J* 38.6), 31.7, 29.1, 29.0, 28.0, 27.6, 22.6 and 14.0; δ_F(376 MHz, $CDCl_3$ from ex. CF_3CO_2H) 6.5 (s, 3 F); *m*/*z* 230 (M + 2), 228 (M^+), 199, 143 and 69 (Found: M^+, 228.0871. $C_{10}H_{16}F_3Cl$ requires *M*, 228.0893).

Typical procedure for Reformatsky reaction of $BrCF_2CO_2Et$ using SmI_2 for the isolation of the 2,2-difluoro-3-hydroxy ester

$BrCF_2CO_2Et$ (1.0 mmol) and octan-2-one (0.9 mmol) in THF was added to a solution of SmI_2 (2.2 mmol) in THF at room temperature under nitrogen. The colour of the solution turned from purple to yellow at once, indicating the end of the reaction. After work-up with 1 M HCl, the mixture was extracted with ether (3 × 10 ml), and the combined organic extracts were washed with water, dried ($MgSO_4$) and evaporated. Purification of the residue with GPC gave the corresponding ester ethyl 2,2-difluoro-3-hydroxy-3-methylnonanoate **6d** (71%) as a colourless oil; δ_H($CDCl_3$) 4.36 (q, 2 H, *J* 7.2), 2.04 (s, 1 H), 1.60 (t, 2 H, *J* 8.1), 1.37 (t, 3 H, *J* 7.2), 1.30–1.47 (m, 8 H), 1.32 (s, 3 H) and 0.89 (t, 3 H, *J* 6.8); δ_C($CDCl_3$) 163.8 (t, *J* 33.1), 116.1 (t, *J* 259), 74.6 (t, *J* 24), 62.9, 35.2, 31.7, 29.7, 22.52, 22.46, 19.7, 14.0 and 13.9; δ_F($CDCl_3$; ppm from external CF_3CO_2H) −40.4 and −42.4 (ABq, *J* 253) (Found: M^+, 252.1509. $C_{12}H_{22}F_3O_3$ requires *M*, 252.1537).

The reaction of 4-*tert*-butylcyclohexanone gave two stereoisomers of ethyl 2,2-difluoro-2-(1′-hydroxy-4′-*tert*-butylcyclohexyl)acetate **6h** in an almost 1:1 ratio, the separation of which was effected by gel-permeation chromatography. Each of the isomers could not be separated completely, but the chemical shifts of the ^1H, ^{13}C and ^{19}F NMR could be determined.

6h Isomer 1: Colourless oil; δ_H($CDCl_3$) 4.34 (q, 2 H, *J* 6.8), 2.29–2.36 and 1.40–1.85 (m, 8 H), 2.15 (s, 1 H), 1.36 (t, 3 H, *J* 6.8), 0.95–1.13 (m, 1 H) and 0.87 (s, 9 H); δ_C($CDCl_3$) 163.8 (t, *J* 31.2), 116.0 (t, *J* 258), 73.3 (t, *J* 23.9), 62.8, 47.2, 32.3, 30.2, 27.4, 21.3 and 13.9; δ_F($CDCl_3$; ppm from external CF_3CO_2H) −43.8 (s, 2 F) (Found: M^+, 278.1650. $C_{14}H_{24}F_2O_3$ requires *M*, 278.1639).

6h Isomer 2: Colourless oil; δ_H($CDCl_3$) 4.35 (q, 2 H, *J* 6.8), 2.48 (s, 1 H), 2.30–2.35 and 1.43–1.83 (m, 8 H), 1.36 (t, 3 H, *J* 6.8), 1.07–1.17 (m, 1 H) and 0.86 (s, 9 H, s); δ_C($CDCl_3$) 163.8 (t, *J* 31.2), 117.4 (t, *J* 261), 72.5 (t, *J* 23.9), 62.9, 46.2, 33.7, 32.3, 27.5, 23.1 and 13.9; δ_F($CDCl_3$; ppm from external CF_3CO_2H) −36.0 (s, 2 F) (Found: M^+, 278.1717. $C_{14}H_{24}F_2O_3$ requires *M*, 278.1639).

Similarly, 2-phenylpropionaldehyde gave the corresponding two diastereoisomers **6c** in the ratio of 1:1.4. These isomers were also separated by gel-permeation chromatography; pure isomer 2 was obtained, but isomer 1 could not be separated from isomer 2 completely.

6c Isomer 1: Colourless oil; δ_H($CDCl_3$) 7.25–7.34 (m, 5 H), 4.25 (q, 2 H, *J* 6.8), 4.21–4.27 (m, 1 H), 3.17 (quint, 1 H, *J* 7.3), 2.38 (br s, 1 H), 1.41 (d, 3 H, *J* 7.3) and 1.32 (t, 3 H, *J* 6.8); δ_C($CDCl_3$) 163.5 (t, *J* 33.1), 141.3, 128.8, 128.3, 127.3, 114.9 (t, *J* 258), 75.2 (t, *J* 23.9), 63.0, 40.5, 18.5 and 13.8; δ_F($CDCl_3$; ppm from external CF_3CO_2H) −32.0 (d, J_{FF} 263, 1 F) and −47.8 (dd, J_{FF} 263, J_{HF} 18.3) (Found: M^+, 258.1099. $C_{13}H_{16}F_2O_3$ requires *M*, 258.1067).

6c Isomer 2: Colourless oil; δ_H($CDCl_3$) 7.23–7.32 (m, 5 H), 4.20–4.34 (m, 1 H), 4.13 (q, 2 H, *J* 6.8), 3.15 (quint, 1 H, *J* 7.1), 2.39 (s, 1 H), 1.40 (d, 3 H, *J* 7.1) and 1.28 (t, 3 H, *J* 6.8); δ_C($CDCl_3$) 163.6 (t, *J* 33.1), 142.9, 128.5, 127.9, 126.9, 114.7 (t, *J* 258), 74.9 (t, *J* 23.9), 63.0, 39.6, 16.2 and 13.8; δ_F($CDCl_3$; ppm from external CF_3CO_2H) −38.5 (dd, J_{FF} 266, J_{HF} 9.2, 1 F), −43.3 (dd, J_{FF} 266, J_{HF} 13.8) (Found: M^+, 258.0974. $C_{13}H_{16}F_2O_3$ requires *M*, 258.1067).

The reaction with benzophenone gave **6g** as colourless crystals from hexane, mp 82.0–82.5 °C (Found: C, 66.63; H, 5.26. $C_{17}H_{16}O_3F_2$ requires C, 66.65; H, 5.28%); δ_H($CDCl_3$) 7.53–7.55 (m, 4 H), 7.29–7.35 (m, 6 H), 4.17 (q, 2 H, *J* 7.0), 3.94 (s, 1 H, OH) and 1.11 (t, 3 H, *J* 7.0); δ_C($CDCl_3$) 164.0 (t, *J* 32.1), 139.6, 128.2, 128.0, 127.3, 114.3 (t, *J* 265), 79.5 (t, *J* 23.9), 63.2 and 13.5; δ_F($CDCl_3$; ppm from external CF_3CO_2H) −33.6 (s, 2 F); *m*/*z* 306 (M^+), 290, 261 and 231.

All the other known products **6a**,[13] **6b**,[14] **6e**,[14] **6f**[13] and **6i**[13] were characterized by ^1H, ^{13}C, ^{19}F NMR and mass spectroscopy.

References

1 D. J. Burton and Z.-Y. Yang, *Tetrahedron*, 1992, **48**, 189; H. Uno and H. Suzuki, *Synlett*, 1993, 91.

2 M. Yoshida, Y. Morinaga and M. Iyoda, *J. Fluorine Chem.*, 1994, **68**, 33; M. Yoshida, M. Ueda, Y. Morinaga, N. Kamigata and M. Iyoda, *Chem. Lett.*, 1992, 227; M. Yoshida, A. Morishima, D. Suzuki and M. Iyoda, *Bull. Chem. Soc. Jpn.*, 1996, **69**, 2019.

3 M. Yoshida, D. Suzuki and M. Iyoda, *Chem. Lett.*, 1994, 2357.

4 H. Lund and N. J. Jensen, *Acta Chem. Scand., Sect. B*, 1974, **28**, 263.

5 G. A. Molander, *Chem. Rev.*, 1992, **92**, 29; D. P. Curran, T. L. Fevig, C. P. Jasperse and M. J. Totleben, *Synlett*, 1992, 943; J. A. Soderquist, *Aldrichimica Acta*, 1991, **24**, 5; J. Inanaga, *J. Synth. Org. Chem. Jpn.*, 1989, **47**, 200.
6 J. Inanaga, M. Ishikawa and M. Yamaguchi, *Chem. Lett.*, 1987, 1485; K. Otsubo, K. Kawamura, J. Inanaga and M. Yamaguchi, *Chem. Lett.*, 1987, 1487; E. Hasegawa and D. P. Curran, *Tetrahedron Lett.*, 1993, **34**, 1717.
7 T. Hagiwara and T. Fuchikami, *Synlett*, 1995, 717; J. Grobe and J. Hegge, *Synlett*, 1995, 641; F. Aymard, J. Y. Nedelec and J. Perichon, *Tetrahedron Lett.*, 1994, **35**, 8623; K. Iseki, T. Nagai and Y. Kobayashi, *Tetrahedron Lett.*, 1994, **35**, 3137; G. K. S. Prakash, D. Deffieux, A. K. Yudin and G. A. Olah, *Synlett.*, 1994, 1057; G. K. S. Prakash, R. Krishnamurti and G. A. Olah, *J. Am. Chem. Soc.*, 1989, **111**, 393; R. Krishnamurti, D. R. Bellew and G. K. S. Prakash, *J. Org. Chem.*, 1991, **56**, 984; G. P. Stahly and D. R. Bell, *J. Org. Chem.*, 1989, **54**, 2873; I. Ruppert, K. Schlich and W. Volbach, *Tetrahedron Lett.*, 1984, **25**, 2195.
8 R. W. Lang, *Helv. Chim. Acta*, 1986, **69**, 881; M. Fujita, T. Morita and T. Hiyama, *Tetrahedron Lett.*, 1986, **27**, 2135; M. Fujita and T. Hiyama, *Bull. Chem. Soc. Jpn.*, 1987, **60**, 4377; A. Solladie-Cavallo and S. Quazzotti, *J. Fluorine Chem.*, 1990, **46**, 221.
9 H. Tanaka, S. Yamashita, Y. Katayama and S. Torii, *Chem. Lett.*, 1986, 2043.
10 T. Shono, N. Kise and H. Oka, *Tetrahedron Lett.*, 1991, **32**, 6577.
11 M. Yoshida, D. Suzuki and M. Iyoda, *Synth. Commun.*, 1996, **26**, 2513.
12 A. Fürster, *Synthesis*, 1989, 571; I. Ishihara, *J. Synth. Org. Chem. Jpn.*, 1992, **50**, 347; T. Taguchi, O. Kitagawa, Y. Suda, S. Ohkawa, A. Hashimoto, Y. Iitaka and Y. Kobayashi, *Tetrahedron Lett.*, 1988, **29**, 5291; O. Kitagawa, T. Taguchi and Y. Kobayashi, *Tetrahedron Lett.*, 1988, **29**, 1803; O. Kitagawa, A. Hashimoto, Y. Kobayashi and T. Taguchi, *Chem. Lett.*, 1990, 1307; D. J. Burton and J. C. Easdon, *J. Fluorine Chem.*, 1988, **38**, 125; T. Tukamoto, T. Yoshiyama and T. Kitazume, *Tetrahedron: Asymmetry*, 1991, **2**, 759.
13 E. A. Hallinan and J. Fried, *Tetrahedron Lett.*, 1984, **22**, 2301.
14 T. T. Curran, *J. Org. Chem.*, 1993, **58**, 6360.
15 J. M. Altenburger and D. Schirlin, *Tetrahedron Lett.*, 1991, **32**, 7255.
16 R. W. Lang and B. Schaub, *Tetrahedron Lett.*, 1991, **32**, 6577.
17 X. Lu, S. Ma and J. Zhu, *Tetrahedron Lett.*, 1988, **29**, 5129; S. Ma and X. Lu, *Tetrahedron*, 1990, **46**, 357.
18 T. Imamoto and M. Ono, *Chem. Lett.*, 1987, 501.
19 T. Kitazume and T. Ikeya, *J. Org. Chem.*, 1988, **53**, 2350.

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