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Fluorination of 2-oxo-ethane derivatives with diethylaminosulfur trifluoride (DAST)

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Abstract

The fluorination of 2-oxo-ethane derivatives with DAST is described. The use of ZnI_2 as a catalyst improves the yield in the fluorination of 2-phenyl-2-oxo-acetonitrile with DAST.

Keywords: Diethylaminosulfur trifluoride; Difluoromethylene compounds; ZnI_2 catalyst; NMR spectroscopy; 2-Oxo-ethane derivatives

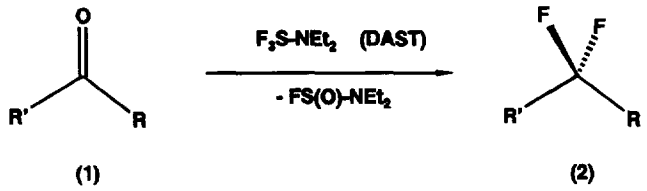
1. Introduction

Diethylaminosulfur trifluoride is a widely used and effective fluorinating agent. It has been predominantly applied to convert alcohols, aldehydes, ketones and glyoxalates into the corresponding monofluoromethyl and difluoromethylene derivatives [1–5]. Less common is the conversion of dialkyl sulfoxides to fluorinated thioethers [6,7], or of cyanohydrins to fluorocyanides [8]. In addition, DAST has been applied to induce rearrangement reactions [9,10]. Furthermore, DAST plays an important role in the synthesis of fluorinated derivatives of natural products, e.g. fluorinated steroids [11], sugars [12], nucleosides and nucleotides [13], and amino acids [14].

2. Results and discussion

We wish to report on the synthesis of several 2-aryl- and 2-alkyl-2,2-difluoroethane derivatives, which might be useful as building blocks for potentially biorelevant organofluorine compounds. Thus, the carbonyl compounds **1** are converted to difluoromethylene derivatives **2** as shown in Scheme 1.

In principle, this reaction was studied in detail by Middleton as early as 1975 [2], but attracted our attention very recently in connection with our studies on C-fluorinated organophosphorus compounds. When R represents hydrogen or functional groups such as carboxylate or nitrile, this reaction leads conveniently to difluorinated toluenes, difluorinated arylacetic acid esters and difluorinated nitriles [15].



R = COOEt, CH(OEt)$_2$, CN; R, R' = Alkyl, Aryl.

Scheme 1.

Middleton and Bingham [5] in 1980 described the synthesis of several 2-aryl-2,2-difluoroacetic acid esters according to Scheme 1, using 2 equiv. of DAST per 1 equiv. of 2-aryl-2-oxo-acetic acid ester. We re-investigated the reaction of 2-phenyl-, 2-(4-fluorophenyl)- and 2-(3-trifluoromethylphenyl)-2-oxo-acetic acid ethyl esters **2a–c** with DAST according to Scheme 2a.

We found that 1 equiv. of DAST is sufficient to convert 1 equiv. of 2-aryl-2-oxo-acetic acid esters, provided that after the initial exothermic phase the reaction mixture is heated for 4 h at 60 °C and then left at room temperature overnight. The 2-aryl-2,2-difluoroacetic acid esters are obtained in good yield as listed in Table 1. Middleton used $CFCl_3$ as an extractant during the aqueous work-up procedure for the reaction mixture. It is adequate to replace $CFCl_3$, an ozone layer damaging fluorochlorocarbon, by CH_2Cl_2. Yields were not reduced when the strongly acidic aqueous phase was neutralised with solid $NaHCO_3$ before extraction with CH_2Cl_2.

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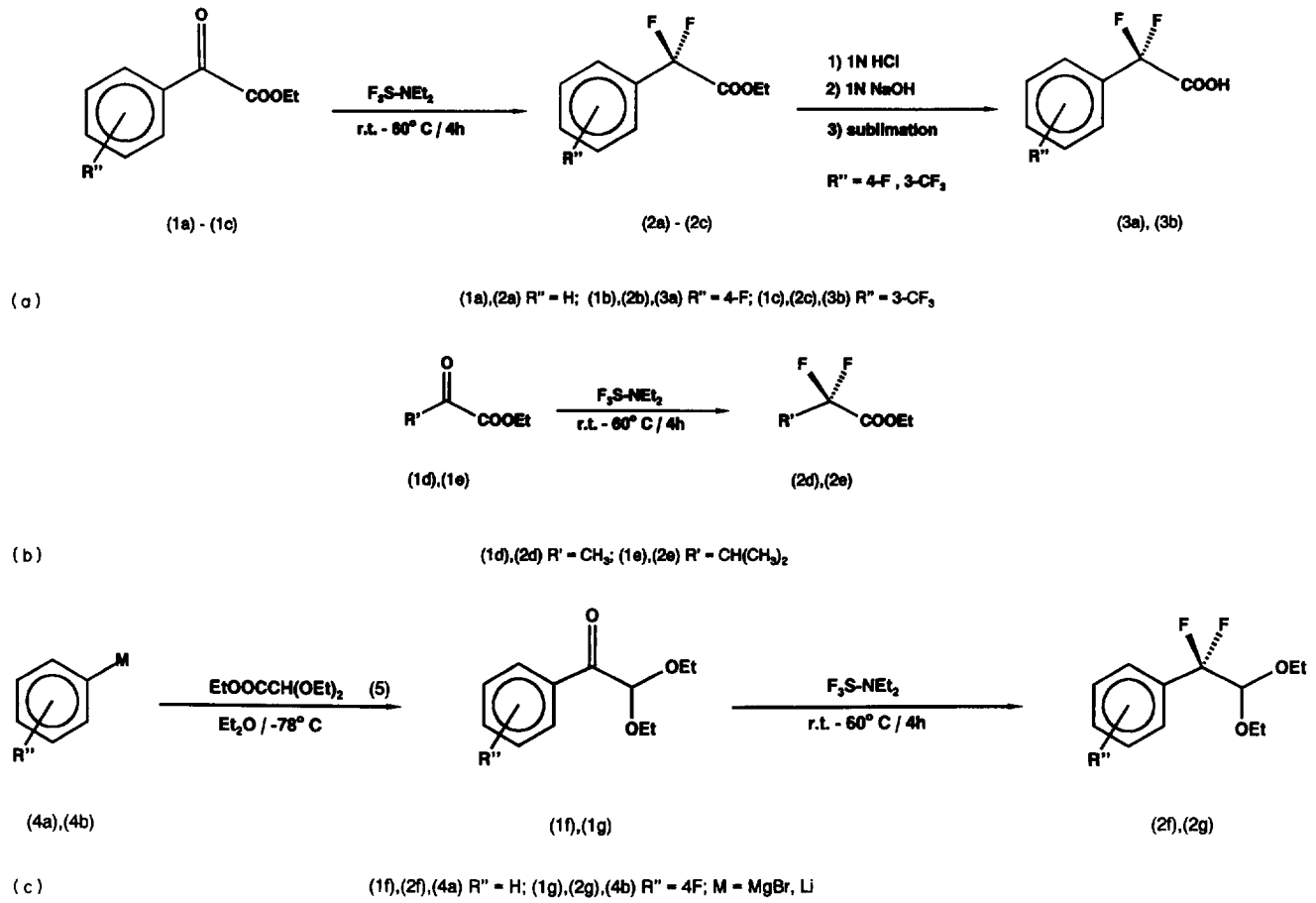


Scheme 2.

The esters **2b** and **2c** were hydrolysed with 1 N NaOH and the resulting reaction mixtures treated with dilute hydrochloric acid [5] (see Scheme 2a). We obtained the 2-aryl-2,2-difluoroacetic acids **3a** and **3b** as yellow oils which partly crystallised upon cooling to 8 °C. Recrystallisation from non-polar solvents like hexane, pentane or ligroin failed. Instead, sublimation of the crude solid/oil mixtures in vacuo afforded the acids **3a** and **3b** as hygroscopic, white, crystalline products as shown in Table 1.

The same fluorination procedure was successfully extended to 2-alkyl-2-oxo-ethane derivatives according to Scheme 2b.

This led to good yields of 2,2-difluoropropionic and isobutyric acid derivatives as shown in Table 1.

2-Phenyl-2,2-difluoroacetaldehyde was synthesised in 1990 by Suga and Schlosser [16] via a multistep procedure including a Pummerer reaction. It is reported to be an unstable product which decomposes rapidly at room temperature. In

Table 1
Novel syntheses of R'–CF_2–R (**2a–h**) by fluorination of R'–CO–R (**1**) with DAST

Compound	R'	R	Yield (%)	b.p. (°C/[torr]), m.p. (°C), subl. (°C/[torr])
2a	C_6H_5	COOEt	75.6	100 [20]
2b	4-F-C_6H_4	COOEt	77.5	83 [0.3]
2c	3-CF_3-C_6H_4	COOEt	7.9	103 [20]
2d	CH_3	COOEt	62.3	33–34 [30]
2e	$(CH_3)_2CH$	COOEt	60.1	55 [20]
2f	C_6H_5	$CH(OEt)_2$	79.4	93 [0.3]
2g	4-F-C_6H_4	$CH(OEt)_2$	77.5	91 [0.3]
2h	C_6H_5	CN	65.3	86 [80]
3a	4-F-C_6H_4	COOH	76.7	51 (m.p.), 70 °C [0.001]
3b	3-CF_3-C_6H_4	COOH	85.5	40 (m.p.), 70 °C [0.001]

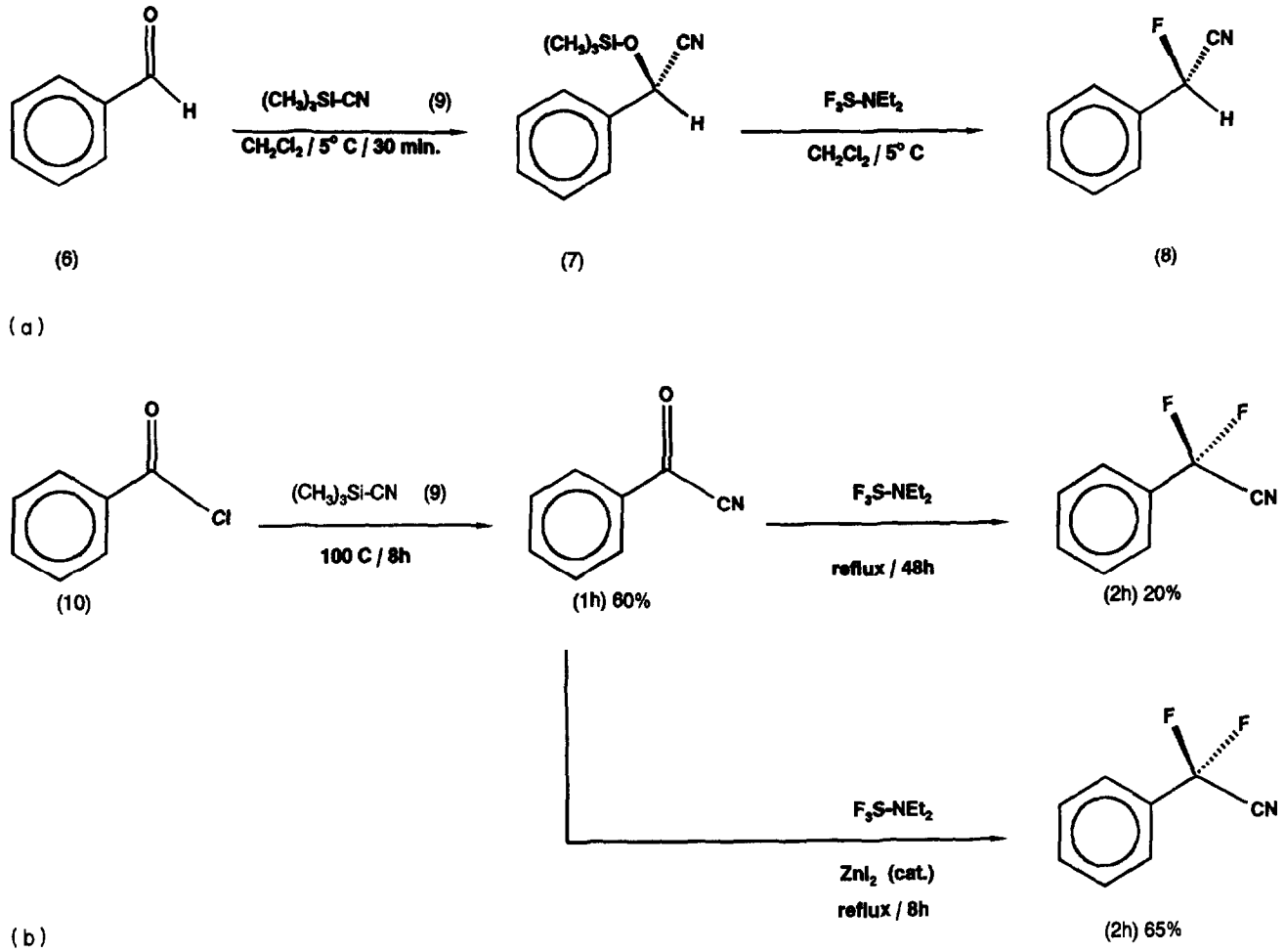
order to avoid this multistep procedure we sought 2-aryl-2-oxo-acetaldehyde derivatives which could be easily converted into 2-aryl-2,2-difluoroacetaldehyde derivatives by Middleton's method. We found that the 2-aryl-2-oxo-acetaldehyde diethylacetals **1f** and **1g** are accessible via the Grignard method or the reaction of the aryllithium compounds **4a** and **4b** with 2,2-diethoxyacetic acid ethyl ester (**5**) at low temperature and react with DAST to yield the 2-aryl-2,2-difluoroacetaldehyde ethylacetals **2f** and **2g** as shown in Scheme 2c.

Since these acetals are stable at room temperature for several months and can be distilled without decomposition, they may serve as a convenient storage form of the unstable 2-aryl-2,2-difluoroacetaldehydes.

All attempts to cleave the 2-aryl-2,2-difluoroacetaldehyde diethylacetals to the free aldehydes with formic acid, trifluoroacetic acid, bromotrimethylsilane and iodotrimethylsilane [17] failed. At ambient temperature and after 1 h to 2 d, only unreacted starting materials were recovered in nearly quantitative yield, as shown by NMR spectroscopy. Strongly acidic conditions and high temperatures resulted in complete decomposition of the 2-aryl-2,2-difluoroacetaldehyde diethylacetals. Further investigations on the cleavage of 2,2-difluorinated aldehyde acetals will be carried out.

The easy and convenient conversion of the aldehydes to the 2-monofluoroacetonitrile **8** with trimethylsilyl cyanide (**9**), (TMSCN) [8] and DAST according to Scheme 3a, and the recently reported two-step procedure [15] obtain 2-aryl-2,2-difluoroacetonitriles **2h** [5] prompted us to investigate the reaction of aromatic acyl chlorides **10** with TMSCN (**9**) and DAST according to Scheme 3b.

Thus, benzoyl chloride (**10**) was refluxed for 8 h with TMSCN (**9**) to yield 2-phenyl-2-oxo-acetonitrile (**1h**), which was not isolated but directly reacted with DAST at reflux temperature for another 8 h. In our hands, this reaction yielded only small amounts of 2-phenyl-2,2-difluoroacetonitrile (**2h**) (12% total yield) even when 2 equiv. of DAST were used and reaction times were increased up to 48 h. In the literature [7] we found several examples that Lewis acids enhance the fluorination power of DAST in cases of less reactive substrates. In our case, we obtained the best results using ZnI_2. By addition of catalytic amounts of ZnI_2 we were able to increase the yield in the reaction of 2-phenyl-2-oxo acetonitrile (**1h**) with DAST to 65% whereas other Lewis



Scheme 3.

acids, e.g. $AlCl_3$ or $SbCl_3$, had no influence on the yield. All results are summarised in Table 1. The 2-oxo-ethane derivatives **2**, used as precursors, were synthesised by well-known standard procedures [18,19].

3. Experimental details

DAST was purchased from Th. Schuchardt & Merck, Darmstadt, Germany. Educts **1a–h** were synthesised according to literature methods [18,19]. NMR samples were prepared as ca. 5% (^{19}F) and 10% (^{1}H) solutions in $CDCl_3$. Acids were measured as 10% solutions in 1 M $DClO_4$ ($HClO_4$ in D_2O). Internal references: TMS and C_6F_6. NMR spectra were recorded on a Bruker AM 200SY spectrometer. The standard sign convention for chemical shifts is used: positive resonance sequences correspond to positive chemical shifts.

*3.1. Fluorination of 2-aryl-2-oxo-ethane derivatives **1a–g** with DAST. General procedure for the synthesis of compounds **2a–g***

A 100 ml Teflon flask fitted with a reflux condenser and a 10 ml dropping funnel (ordinary laboratory glass) was carefully dried and saturated with nitrogen. In the Teflon flask were placed 46 mmol of the corresponding 2-aryl- or 2-alkyl-2-oxo-ethane derivative. Via the dropping funnel, 46 mmol of DAST (7.41 g, 6.1 ml) were added dropwise. In the case of 2-aryl- and 2-alkyl-2-oxo-acetic acid esters **1a–e** the temperature increased to 55 °C, whereas no exothermic effect was observed in the fluorination of acetals **1f** and **1g**. After cooling to room temperature, the reaction mixture was heated for 4 h to 60 °C. The reaction mixture was then poured into 200 ml of ice-water. After the addition of 100 ml of CH_2Cl_2, the organic and the aqueous phase were separated. The organic phase was subsequently washed with 50 ml of saturated aq. $NaHCO_3$ and three times with 50 ml of saturated aq. NaCl solution. The aqueous phase was neutralised with solid $NaHCO_3$ and extracted three times with 50 ml of CH_2Cl_2. The CH_2Cl_2 phases were washed with 50 ml of saturated NaCl solution. The combined organic phases were dried over Na_2SO_4. Evaporation of the solvent afforded light yellow oils which were distilled in vacuo.

2-Phenyl-2,2-difluoroacetic acid ethyl ester (**2a**): Yield, 75.6%; b.p. 100 °C/20 Torr. ^{1}H NMR (10% $CDCl_3$/TMS) δ: 7.64–7.59 (2H arom., m); 7.48–7.44 (3H arom., m); 4.28 (2H, q., $^{3}J_{HH}$ = 7.1 Hz); 1.29 (3H, t., $^{3}J_{HH}$ = 7.1 Hz) ppm. ^{19}F NMR (5% $CDCl_3/C_6F_6$) δ: 57.97 (s) ppm. Analysis: Calc. for $C_{10}H_{10}F_2O_2$: C, 59.98; H, 5.04%. Found: C, 59.95; H, 5.00%.

2-(4-Fluorophenyl)-2,2-difluoroacetic acid ethyl ester (**2b**): Yield, 77.5%; b.p. 83 °C/0.3 Torr. ^{1}H NMR (10% $CDCl_3$/TMS) δ: 7.71–7.66 (2H arom., m.); 7.23–7.14 (2H arom., m.); 4.33 (2H, q., $^{3}J_{HH}$ = 7.2 Hz); 1.31 (3H, t., $^{3}J_{HH}$ = 7.2 Hz) ppm. ^{19}F NMR (5% $CDCl_3/C_6F_6$) δ: 58.81 (2F, s.); 52.81 (1F, m.) ppm. Analysis: Calc. for $C_{10}H_9F_3O_2$: C, 55.03; H, 4.16%. Found: C, 55.10; H, 4.12%.

2-(3-Trifluoromethylphenyl)-2,2-difluoroacetic acid ethyl ester (**2c**): Yield, 72.9%; b.p. 103 °C/0.3 Torr. ^{1}H NMR (10% $CDCl_3$/TMS) δ: 7.89–7.57 (4H arom., m.); 4.32 (2H, q., $^{3}J_{HH}$ = 7.1 Hz); 1.32 (3H, t., $^{3}J_{HH}$ = 7.1 Hz) ppm. ^{19}F NMR (5% $CDCl_3/C_6F_6$) δ: 98.97 (3F, s.), 57.76 (2F, s.) ppm. Analysis: Calc. for $C_{11}H_9F_5O_2$: C, 49.24; H, 3.38%. Found: C, 49.35; H, 3.40%.

2,2-Difluoropropanoic acid ethyl ester (**2d**): Yield, 62.3%, b.p. 33–34 °C/30 Torr. ^{1}H NMR (10% $CDCl_3$/TMS) δ: 4.26 (2H, q., $^{3}J_{HH}$ = 7.2 Hz); 1.74 (3H, t., $^{3}J_{FH}$ = 18.8 Hz); 1.29 (3H, t., $^{3}J_{HH}$ = 7.2 Hz) ppm. ^{19}F NMR (5% $CDCl_3/C_6F_6$) δ: 62.72 (2F, q., $^{3}J_{FH}$ = 18.8 Hz) ppm. Analysis: Calc. for $C_5H_8F_2O_2$: C, 43.46; H, 5.84%. Found: C, 43.55; H, 5.90%.

2,2-Difluoro-3-methylbutanoic acid ethyl ester (**2e**): Yield, 60.1%; b,p. 55 °C/20 Torr. ^{1}H NMR (10% $CDCl_3$/TMS) δ: 4.25 (2H, q., $^{3}J_{HH}$ = 7.2 Hz); 2.29 (1H, m., $^{3}J_{HH}$ = 7.2 Hz, $^{3}J_{FH}$ = 14.47 Hz); 1.28 (3H, t., $^{3}J_{HH}$ = 7.2 Hz); 0.97 (6H, d., $^{3}J_{HH}$ = 7.2 Hz) ppm. ^{19}F NMR (5% $CDCl_3/C_6F_6$) δ: 47.29 (2F, d., $^{3}J_{FH}$ = 14.74 Hz) ppm. Analysis: Calc. for $C_7H_{12}F_2O_2$: C, 50.58; H, 7.28%. Found: C, 50.60; H, 7.24%.

2-Phenyl-2,2-difluoroacetaldehyde diethylacetal (**2f**): Yield, 79.4%; b.p. 93 °C/0.3 Torr. ^{1}H NMR (10% $CDCl_3$/TMS) δ: 7.60–7.34 (5H arom., m.); 4.65 (t., 1H, $^{3}J_{FH}$ = 4.7 Hz); 3.85–3.55 (4H, m., $^{2}J_{HH}$ = −9.3 Hz, $^{3}J_{HH}$ = 7.1 Hz); 1.22 (6H, $^{3}J_{HH}$ = 7.1 Hz) ppm. ^{19}F NMR (5% $CDCl_3/C_6F_6$) δ: 54.94 [m. (broad, indicating hindered rotation)] ppm. Analysis: Calc. for $C_{12}H_{16}F_2O_2$: C, 62.60; H, 7.00%. Found: C, 63.00; H, 7.12%.

2-(4-Fluorophenyl)-2,2-difluoroacetaldehyde diethylacetal (**2g**): Yield, 77.5%; b.p. 91 °C/0.3 Torr. ^{1}H NMR (10% $CDCl_3$/TMS) δ: 7.56–7.49 (2H, m.); 7.25–7.03 (2H, m.); 4.65 (1H, t., $^{3}J_{FH}$ = 4.7 Hz); 3.84–3.61 (4H, m., $^{2}J_{HH}$ = −9.4 Hz, $^{3}J_{HH}$ = 7.0 Hz); 1.22 (6H, t., $^{3}J_{HH}$ = 7.0 Hz) ppm. ^{19}F NMR (5% $CDCl_3/C_6F_6$) δ: 55.30 (broad, indicating hindered rotation), 2F, m.]; 50.44 (1F, m.) ppm. Analysis: Calc. for $C_{12}H_{15}F_3O_2$: C, 58.04; H, 6.09%. Found: C, 58.22; H, 6.07%.

*3.2. Hydrolysis of 2-aryl-2,2-difluoroacetic acid ethyl esters **2b and 2c***

*Synthesis of 2-aryl-2,2-difluoroacetic acids **3a and 3b** [5]*

2-Aryl-2,2-difluoroacetic ethyl ester (27 mmol) was mixed with 37 ml of 1 N NaOH and stirred for 24 h at room temperature. After the addition of 37 ml of 1 N HCl, the aqueous phase was extracted three times with 100 ml of CH_2Cl_2. The organic phase was washed with 200 ml of saturated aq. NaCl solution and dried over Na_2SO_4. After evaporation of the solvent, the partly crystallised oil was sublimed in vacuo at 0.001 Torr and 70–80 °C.

2-(4-Fluorophenyl)-2,2-difluoroacetic acid (**3a**): Yield, 76.7%; subl. temp. 75 °C/0.001 Torr. ^{1}H NMR (10% $DClO_4$) δ: 7.66–7.757 (2H, m.); 7.31–7.16 (2H, m.) ppm.

^{19}F NMR (10% $DClO_4$) δ: 58.81 (2F, s.); 52.88–52.75 (1F, m.) ppm. Analysis: Calc. for $C_8H_6F_2O_2$: C, 55.80; H, 3.51%. Found: C, 55.53; H, 3.45%.

2-(3-Trifluoromethylphenyl)-2,2-difluoroacetic acid (**3b**): Yield, 71.2%; subl. temp. 79 °C/0.001 Torr. ^1H NMR (10% $DClO_4$) δ: 10.33 (1H, s., COOH); 7.89–7.58 (4H arom., m.) ppm. ^{19}F NMR (10% $DClO_4$) δ: 98.84 (3F, s.); 65.94 (2F, s.) ppm. Analysis: Calc. for $C_9H_5F_5O_2$: C, 45.02; H, 2.10%. Found: C, 44.95; H, 2.19%.

*Synthesis of 2-phenyl-2,2-difluoroacetonitrile (**2h**)*

Benzoic acid chloride (2.4 g, 19 mmol, 1.98 ml), 1.9 g (19 mmol, 2.5 ml) of cyanotrimethylsilane (TMSCN) [19] and 40 mg of ZnI_2 (catalyst) [19] were heated with exclusion of moisture for 8 h at 100 °C. After the solution had cooled down to room temperature, 20 mg of ZnI_2 and subsequently 6 g (37 mmol) of DAST were added at 5 °C (ice bath). When addition was complete, the reaction mixture was refluxed for another 8 h. The reaction mixture was poured into 200 ml of ice-water and extracted with 100 ml of CH_2Cl_2. After separation of the organic and aqueous phases, the aqueous phase was neutralised with solid $NaHCO_3$ and extracted three times with 50 ml of CH_2Cl_2. The organic phase was subsequently washed with saturated aq. $NaHCO_3$ and saturated aq. NaCl solutions and dried over Na_2SO_4. Evaporation of the solvent afforded an intensively yellow coloured liquid which was distilled in vacuo (80 Torr).

2-Phenyl-2,2-difluoroacetonitrile (**2h**): Yield, 65.3%; b.p. 86 °C/80 Torr. ^1H NMR (10% $CDCl_3$/TMS) δ: 8.20–8.13 (2H arom., m.); 7.84–7.75 (1H arom., m.); 7.69–7.57 (2H arom., m.) ppm. ^{19}F NMR (5% $CDCl_3/C_6F_6$) δ: 78.71 (s.) ppm. Analysis: Calc. for $C_8H_5F_2N$: C, 62.73; H, 3.29; N, 9.15%. Found: C, 62.78; H, 3.25; N, 9.09%.

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