1,1-Dichloro-2,2,2-trifluoroethyllithium in Asymmetric Synthesis, II. A Route to Optically Pure 4,4,4-Trifluoro-2-hydroxybutanoic Acid

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On addition of pre-cooled butyllithium to 1,1,1-trichloro-2,2,2-trifluoroethane **(1)** in diethyl ether at −125°C, 1,1-dichloro-2,2,2-trifluoroethyllithium **(2)** is formed, addition of *o*-substituted benzaldehydes yields 1-aryl-2,2-dichloro-3,3,3-trifluoropropanols, whilst addition of the chiral chromium complexes of substituted benzaldehydes yields optically pure alcohols in high yield. After decomplexation, dechlorination, protection and oxidation, optically pure (*S*)-2-tert-butyldimethylsiloxy-4,4,4-trifluorobutanoic acid was obtained.

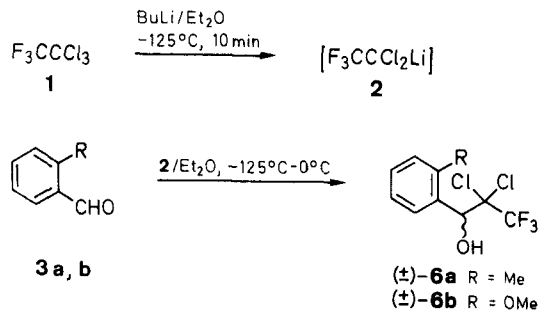
During our work on the enantioselective synthesis of chiral polyfluoro alcohols[1,2] we became interested in the use of 1,1,1-trichloro-2,2,2-trifluoroethane **(1)** which is a precusor for the 1,1,1-trifluoroethyl group (CF_3CH_2).

Previous work[3] has shown that 1,1-dichloro-2,2,2-trifluoroethyllithium **(2)** generated *in situ* (in the presence of the carbonyl compound) from **1** and butyllithium results in mixtures and unsatisfactory yields (~40% isolated).

We report herein the synthesis of optically pure 2,2-dichloro-3,3,3-trifluoropropyl alcohols in high yield (60–80% isolated), as a route to optically pure 3,3,3-trifluoropropyl alcohols **7** and 4,4,4-trifluoro-2-hydroxybutanoic acid derivative (*S*)-**9**.

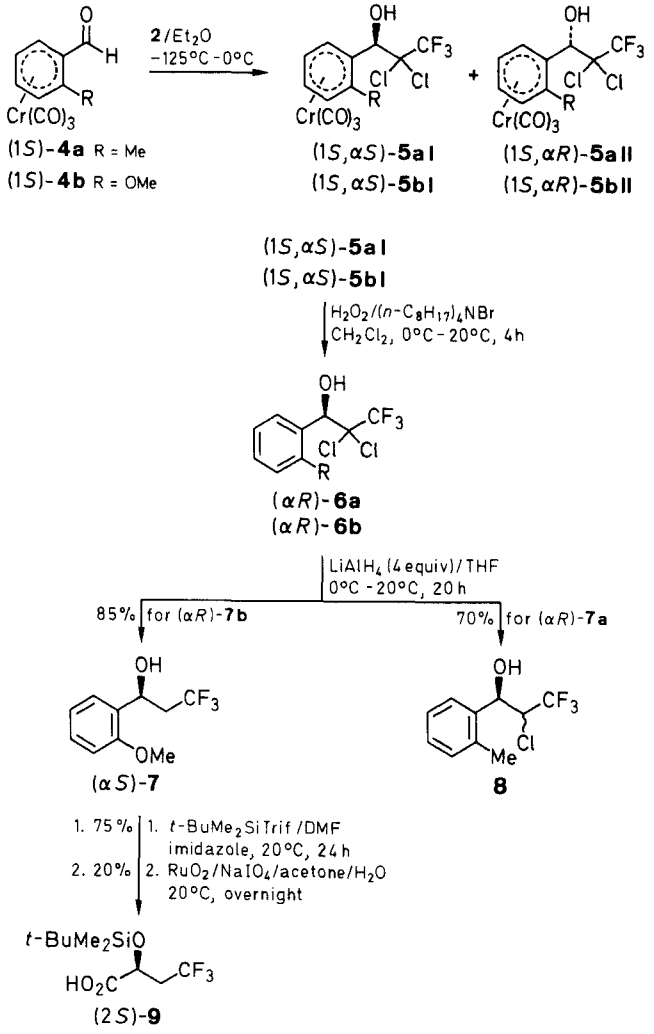
Polyfluoroorganolithium compounds undergo rapid decomposition. For example, formation of 1,1-dichloro-2,2,2-trifluoroethyllithium **(2)** is known to require very low temperatures (−130° to −140°C) and special solvent mixtures, such as dimethyl ether/tetrahydrofuran; it reacts with trimethylchlorosilane or acetone in 60 and 35% yield, respectively.[4] The corresponding *in situ* method lead to mixtures of products.[3]

We found that 1,1-dichloro-2,2,2-trifluoroethyllithium **(2)** could be formed by the addition of a pre-cooled solution of butyllithium to 1,1,1-trichloro-2,2,2-trifluoroethane **(1)** in diethyl ether at −125°C. Care must be taken to ensure that the temperature of the reaction does not rise above −120°C. The thus formed polyfluoroorganolithium **2** can be kept for 10–15 min at this temperature, this is long enough to allow addition of a pre-cooled solution of the substituted benzaldehyde **3a, b** yielding racemic alcohols **6a, b**.



The good yields of alcohols **6** (93–97%) obtained prior to purification, using only one equivalent of each reagent (method A), suggests that the lithium derivative **2** is formed in quantitative yields under those conditions. No byproducts were detected, but traces of decomplexed products were found when complexed aldehydes **4** were used.

The reaction was next performed using the racemic chiral chromium complexes of substituted benzaldehydes **4a–b** leading to the complexed alcohols **5a–b** in good yield (68–80%). and with a satisfying diastereoselectivity (**I/II** = 87–90/13–10) as determined by ^{1}H-NMR.
This asymmetric induction (74–80%) would be expected for *ortho*-substituted complexes of this type.[5–7]
When the optically pure (1*S*) complexes **4a–b** were used then optically pure alcohols **5aI** and **5bI** were isolated (60% and 76%) thus providing, after decomplexation (63–66% yield using hydrogen peroxide/tetraoctylammonium bromide), optically pure alcohols **6a–b**.



According to our model of approach[7,8] the expected configuration of **5aI** and/or **5bI** would be (1*S*,α*S*) thus leading to the *R*-alcohols **6a, b**.
It is important to note the inversion of the optical rotation between (1*S*,α*S*)-**5a** ($[\alpha]_D + 79°$) and (1*S*,α*S*)-**5b** ($[\alpha]_D - 74°$). This is a known and understood phenomenon in arene-chrominum-tricarbonyl complexes; it occurs when the presence of an H-bond changes the nature of the major conformation.[7,9]

The usual method for the dechlorination of polychloropolyfluoro compounds is treatment with zinc powder in an aprotic solvent,[10] however dechlorination of alcohols of type **6** leads to olefinic products.[11,12] Therefore the dechlorination was performed with 2 or 4 equivalents of lithium aluminum hydride in tetrahydrofuran (Table 4). The alcohol (α*R*)-**6b** was quantitatively converted to (α*S*)-**7** with no byproducts. However, (α*R*)-**6a** gave a mixture of products; the major product being a mixture of diastereoisomeric chlorohydrins **8**.

Protection of (α*S*)-**7** as the *tert*-butyldimethylsilyl ether and subsequent oxidation with ruthenium tetroxide gave (*S*)-4,4,4-trifluoro-2-hydroxybutanoic acid [(*S*)-**9**]. According to our hypothesis that the configuration of **6b** is α*R* then the resultant acid **9** would be expected to be *S*. The configuration of (*S*)-**9**, is consistant with the Brewster rules.[13]

1,1,1-Trichloro-2,2,2-trifluoroethane was a gift from Ciba Geigy AG. $LiAlH_4$ was purchased from Janssen und BuLi solution from Merck AG. THF was distilled from Na/benzophenone and Et_2O from $LiAlH_4$. Uncomplexed aldehydes were purchased from Aldrich Chemical Co. and they were used without further purification. Racemic complexed aldehydes were obtained by thermal complexation in dibutyl ether,[14] resolution through the semioxamazone derivatives[15] gave us enantiomerically pure complexed aldehydes. ^{1}H-NMR and ^{13}C-NMR spectra were obtained using a Bruker WP-SY 200 and a Bruker AC 200. ^{19}F-NMR were recorded on a Bruker AM 400. IR spectra were obtained using a Perkin-Elmer 254 IR spectrophotometer. Rotations of optically active compounds were measured on a Perkin-Elmer 241 MC polarimeter. TLC plates and silica gel were purchased from Merck AG.

Reaction of Carbonyl Compounds 3 and 4 with 1,1-Dichloro-2,2,2-trifluoroethyllithium; General Procedure:
Method A: 1,1,1-Trichloro-2,2,2-trifluoroethane (**1**, 563 mg, 360 mL, 3 mmol) is dissolved in anhydrous Et_2O (40 mL). The solution is cooled to −125 °C (N_2/pentane) and a pre-cooled 1.6 M solution of BuLi in hexane (1.88 mL, 3 mmol) is added slowly. The temperature must not rise above −120 °C. After stirring at −125 °C for 10 min, a pre-cooled solution of the desired aldehyde (**3a, b, 4a, b**, 3 mmol) in anhydrous Et_2O (3 mL) is added dropwise at a moderate rate. The reaction mixture is stirred while the temperature is allowed to reach 0 °C. After quenching at 0 °C with 10% HCl (3 mL), the organic phase is separated, washed with brine (6 × 25 mL), to neutrality and dried ($MgSO_4$). The solvent is evaporated at reduced pressure and the crude reaction mixture is purified by flash chromatography on silica gel (15 cm × 5 cm, 70–230 mesh), (Tables 1, 2, 4).

Method B: As for Method A, but using 1.5 equiv. each of 1,1,1-trichloro-2,2,2-trifluoroethane and BuLi (Tables 1, 2, 4).

Decomplexation of Chromium Complexes 5; General Procedure:
To the complexed alcohols **5a, b** (1.8 mmol) dissolved in CH_2Cl_2 (20 mL) and cooled to 0 °C is added H_2O_2 (30 volumes 15 mL). Tetraoctylammonium bromide (50 mg, 0.18 mmol) is added and

Table 1. Addition of **3a, b** to **2**

Substrate	Method	Product	Yield[a] (%)	R_f	Molecular Formula[b]
3a	A	*rac*-**6a**	93 (77)	0.12[c]	$C_{10}H_9Cl_2F_3O$ (273.1)
	B		100 (85)		
3b	A	*rac*-**6b**	97 (43[d])	0.44[e]	$C_{10}H_9Cl_2F_3O_2$ (289.1)
	B		100 (85)		

[a] Crude yield, isolated yield in parenthesis.
[b] Satisfactory microanalyses obtained: C ±0.34, H ±0.04.
[c] Silica gel, solvent: diethyl ether/hexane, 10:90.
[d] Although the crude yield of product was high (97%), difficulties were enconnted during chromatographic separation of the starting material **3b** and **6b**.
[e] Silica gel, solvent: Et_2O/hexane, 20:80.

Table 2. Addition of **4a, b** to **2**

Substrate	Method	Yield[a] (%)	Product: Diastereomer Ratio **5I/5II**	Isolated Yield (%) (1*S*, α*S*)-**5I**
rac-**4a**	A	91 (80)	87:13[b]	
rac-**4b**	A	74 (68)	90:10[b]	
(1*S*)-**4a**	B	94	90:10[c]	60
(1*S*)-**4b**	B	100	96:4[c]	76

[a] Crude yield, isolated yield in parenthesis.
[b] Each diastereomer is racemic.
[c] Each diastereomer is optically pure.

Table 3. Compounds **5, 6** Prepared

Compound	$[\alpha]_D$ (*c*, $CHCl_3$)	R_f (Et_2O/hexane)[a]
(1*S*, α*S*)-**5a**	+79 (1.4)	0.46 (30:70)
(1*S*, α*S*)-**5b**	−74 (0.59)	0.42 (30:70)
(α*R*)-**6a**	−83 (4.1)	0.33 (20:80)
(α*R*)-**6b**	−40 (0.5)	0.28 (20:80)

[a] Silica gel.

Table 4. Dechlorination of **6** with $LiAlH_4$/THF

Substrate	$LiAlH_4$ (equiv)	Recovered Substrate (%)	Products (%)[a]	
			7	**8 (I/II)**
(α*R*)-**6a**	2	43	22	39 (7:3)
	4	6	26	70 (7:3)
(α*R*)-**6b**	2	52	9	39 (6:4)
	4	0	100	0

[a] Mixture of diasteromers as determined by ^{1}H-NMR (200 MHz).

Table 5. Spectroscopic Data of Compounds **5** and **6** Prepared

Product	IR ($CHCl_3$) ν (cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS)[a] δ, J (Hz)	^{13}C-NMR ($CDCl_3$/TMS)[b] δ, J (Hz)
6a	3600, 3550	2.46 (s, 3H, CH_3), 2.7 (d, 1H, ^3J = 5.6, OH), 5.64 (d, 1H, ^3J = 5.6, OH), 7.3 (m, 3H_{arom}), 7.8 (m, 1H_{arom})	20.6 (CH_3), 72.0 (CHOH), 88.5 (q, $^2J_{C-F}$ = 32, CCl_2), 123.1 (q, $^1J_{C-F}$ = 284, CF_3), 126.1, 128.0, 130.0, 131.2 (each CH_{arom}), 135.6, 137.6 (each C_{arom})
6b[c]	3590, 3470	3.89 (s,3H, OCH_3), 4.02 (d, 1H, ^3J = 7.6, OH), 5.62 (d, 1H, ^3J = 7.6, CH), 6.96 (d, 1H_{arom}, ^3J = 7.6), 7.03 (td, 1H_{arom}, ^3J = 7.6, ^4J = 1.7), 7.39 (td, 1H_{arom}, ^3J = 7.6, ^4J = 1.7), 7.52 (dd, 1H_{arom}, ^3J = 7.6, ^4J = 1.7)	55.5(OCH_3), 73.9 (CHOH), 88.8 (q,$^2J_{C-F}$ = 30, CCl_2), 111.2, 120.5 (each (H_{arom}), 122.4 (q, $^1J_{C-F}$ = 283.8, CF_3), 123.8 (C_{arom}), 130.4, 130.5 (each CH_{arom}), 157.7 (C_{arom})
(1*S*, α*S*)-**5a**		2.34 (s, 3H, CH_3), 2.70 (d, 1H, ^3J = 3.8, OH), 5.07 (dd, 1H_{arom}, ^3J = 6.6), 5.21 (d, 1H, ^3J = 3.8, CH), 5.26 (td, 1H_{arom}, ^3J = 6.6, ^4J = 1.0), 5.57 (td, 1H_{arom}, ^3J = 6.6, ^4J = 1.0), 6.09 (dd, 1H_{arom}, ^3J = 6.6, ^4J = 1.0)	–
(1*S*, α*S*)-**5b**[d]	3590, 3300, 1975, 1895	2.62 (d, 1H, ^3J = 3.8, OH), 3.79 (s, 3H, CH_3), 4.98 (t, 1H_{arom}, ^3J = 6.8), 5.02 (d, 1H_{arom}, ^3J = 6.8), 5.52 (d, 1H, ^3J = 3.8, CH), 5.65 (td, 1H_{arom}, ^3J = 6.8, ^4J = 1.4), 6.17 (dd, 1H_{arom}, ^3J = 6.8, ^4J = 1.4)	56.5 (OCH_3), 68.5 (CHOH), 72.8 (CH_{arom}), 87.7 (q, $^2J_{C-F}$ = 32.6, CCl_2), 84.5, 95.3, 96.2 (each CH_{arom}), 97.6 (C_{arom}), 122.6 (q, $^1J_{C-F}$ = 284.3, CF_3), 143.6 (C_{arom}), 232.7 (C≡O)

[a] 200 MHz.
[b] 50 MHz.
[c] ^{19}F-NMR (376 MHz, $CDCl_3$/CCl_3F): δ = −75.04.
[d] ^{19}F-NMR (376 MHz, $CDCl_3$/CCl_3F): δ = −75.6.

vigorous stirring is maintained for 4 h while the temperature is allowed to reach 20 °C. The phases are separated and the aqueous layer is extracted with CH_2Cl_2 (10 mL). The combined organic phases are dried ($MgSO_4$). After evaporation of the solvent under vaccum the crude product is purified by flash chromatography on silica gel (15 cm × 4 cm, 70–230 mesh), (Table 2).

o-[(*S*)-3,3,3-Trifluoro-1-hydroxypropyl]anisole (α*S*)-7:
$LiAlH_4$ (76 mg, 2 mmol) is suspended in anhydrous THF (3 mL), after cooling to 0 °C a solution of (α*R*)-**6b** (145 mg, 0.50 mmol) in anhydrous THF (2 mL) is added. Stirring is maintained for 20 h and the temperature allowed to reach 20 °C. After cooling again, sat. Na_2SO_4 (0.52 mL) is added slowly. Stirring is continued at 20 °C until a white precipitate is formed. After addition of $MgSO_4$ the mixture is heated for 5 min and then filtered. The precipitate must be rinced carefully. The solution is concentrated under reduced pressure and the resulting crude oil is purified by flash chromatography on silica gel (15 cm × 3 cm, 70–230 mesh); yield: 94 mg (85%); $[\alpha]_D^{22}$ −22° (*c* = 1.1, $CHCl_3$); R_f = 0.25 (silica gel, Et_2O/hexane, 20:80).

$C_{10}H_{11}F_3O_2$ (220.2) calc. C 54.55 H 5.04 found 54.23 5.16

IR ($CHCl_3$): ν = 3600 (OH), 3550 cm^{-1} (OH).

^{1}H-NMr (200 MHz, $CDCl_3$/TMS): δ = 2.60 (m, 2H, CH_2, AB-part of an ABM_3X), 2.73 (d, 1H, ^3J = 6.0 Hz, OH), 3.90 (s, 3H, CH_3), 5.24 (q, 1H, $^3J_{H,OH}$ = 6.0 Hz, CH), 6.91 (d, $^1H_{arom}$, ^3J = 7.5 Hz), 7.00 (t, 1H_{arom}, ^3J = 7.5 Hz), 7.35 (m, 2H_{arom}).

^{13}C-NMR (50 MHz, $CDCl_3$/TMS): δ = 41.03 (q, $^2J_{C,F}$ = 27.0 Hz, CH_2), 55.20 (CH_3), 65.58 (q, $^3J_{C,F}$ = 3.5 Hz, CH), 110.52, 120.91 (each CH_{arom}), 126.60 (q, $^1J_{C,F}$ = 275.0 Hz, CF_3), 126.78, 129.08 (each, CH_{arom}), 130.03, 156.05 (each C_{arom})

^{19}F-NMR (376 MHz, $CDCl_3$/$CfCl_3$): δ = −64.23 (t, $^3J_{H,F}$ = 10.7 Hz).

(*S*)-2-*tert*-Butyldimethylsiloxy-4,4,4-trifluorobutanoic Acid (*S*)-9:
o-[(S)-1-tert-Butyldimethylsiloxy-3,3,3-trifluoropropyl]anisole:
Alcohol (α*R*)-**6b** (100 mg, 0.46 mmol) is dissolved in anhydrous DMF (3 mL). After addition of *tert*-butyldimethylsilyl triflate (212 mL, 0.92 mmol) and imidazole (125 mg; 1.84 mmol), the solution is stirred at 20 °C for 24 h. Sat. NH_4Cl (3 mL) is added at 0 °C and, after addition of H_2O (20 mL), the mixture is extracted with Et_2O/hexane, 1:1 (4 × 10 mL). The combined organic layers are dried ($MgSO_4$) and after evaporation of the solvent under reduced pressure the crude oil is purified by flash chromatography on silica gel (15 cm × 2 cm, 70–230 mesh, eluent Et_2O/hexane, 20:80); yield: 115 mg (75%); $[\alpha]_D$ −50° (*c* = 0.90, $CHCl_3$); R_f = 0.73 (silica gel, Et_2O/hexane, 20:80).

^{1}H-NMR (200 MHz, $CDCl_3$/TMS): δ = −0.17 (s, 3H, $SiCH_3$), 0.53 (s, 3H, $SiCH_3$), 0.90 (s, 9H, SiBu-*t*), 2.45 (AB part of an ABM_3X system, 2H, CH_2), 3.85 (s, 3H, CH_3), 5.43 (t, 1H, CH), 6.85 (dd, 1H_{arom}, ^3J = 7.5, ^4J = 1.5 Hz), 6.98 (td, 1H_{arom}, ^3J = 7.5, ^4J = 1.5 Hz), 7.27 (td, 1H_{arom}, ^3J = 7.5, ^4J = 1.5 Hz), 7.50 (dd, 1H_{arom}, ^3J = 7.5, ^4J = 1.5 Hz).

^{19}F-NMR (376 MHz, $CDCl_3$/$CFCl_3$): δ = −63.72 (t, $^3J_{H,F}$ = 10.7 Hz).

(S)-2-tert-Butyldimethylsiloxy-4,4,4-trifluorobutanoic Acid (S)-9
To a suspension of RuO_2 (110 mg, 0.33 mmol) in acetone (5 mL) is added a solution of $NaIO_4$ (267 mg, 1.25 mmol) in H_2O (1.5 mL). The previously formed silyl ether (110 mg, 0.33 mmol) in acetone (10 mL) is then added and the reaction mixture is stirred for 30 min at 20 °C. Then a solution of $NaIO_4$ (1.1 g, 4.95 mmol) in acetone/water (1:1, 12 mL) is added very slowly and stirring is maintained overnight at 20 °C. After addition of isopropyl alcohol (3 mL) the mixture is stirred for another 1 h. After filtration on Celite (1 mm height) and evaporation of the solvent under vacuum the residue is purified by preparative TLC (silica gel eluent Et_2O/hexane 50:50), R_f = 0.24; yield: 18 mg (20%); $[\alpha]_{450}^{20}$ +10° (*c* = 0.6, $CHCl_3$).

IR ($CHCl_3$): ν = 1725 cm^{-1} (CO).

^{1}H-NMR (200 MHz, $CDCl_3$/TMS): δ = 0.10 (2 s, 6H, CH_3), 0.90 (s, 9H, SBn-*t*), 2.65 (m, 2H, AB part of ABM_3X, CH_2), 5.38 (dd, 1H, X part of ABM_3X, CH).

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