

Nucleophilic substitution of optically active 1-alkoxypolyfluoroalkyl sulfonates

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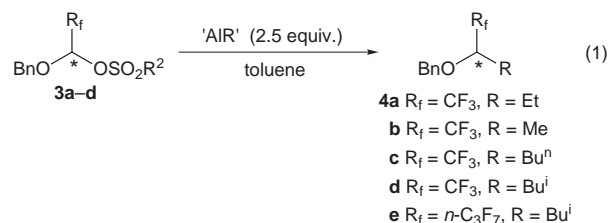
Reaction of 1-alkoxypolyfluoroalkyl sulfonates with lithium tetraalkylaluminates gives stereospecifically alkylated products with a high degree of inversion of configuration; in contrast, the ees of the resulting ethers are slightly reduced in the reaction with trialkylaluminium reagents.

Chiral acetals are versatile building blocks for the synthesis of biologically active agents and functional materials.¹ However, few optically pure compounds are known whose acetal carbon only is chiral.² We have recently reported that the Baeyer–Villiger reaction of optically active α -alkoxyalkyl ketones affords optically active 1-alkoxyalkyl carboxylates. The resulting acetals undergo the substitution reaction with lithium dialkylcuprates in the presence of $\text{BF}_3 \cdot \text{OEt}_2$ to give optically active alkoxyalkanes with inversion of configuration.³ We undertook to expand the concept to trifluoroacetaldehyde because fluorinated chiral compounds are receiving increasing attention in view of their remarkable biological and physical properties.⁴ Furthermore, the nucleophilic C–C bond-forming substitution reaction at a carbon bearing a trifluoromethyl group with inversion of configuration is unprecedented.^{5,6} We report herein a nucleophilic substitution of optically active 1-alkoxy-polyfluoroalkyl sulfonates with an organoaluminium reagent⁷ to give optically active alkoxy-polyfluoroalkanes with a high degree of inversion of configuration.

Optically active 1-alkoxypolyfluoroalkyl sulfonates were prepared according to Scheme 1. Trifluoroacetaldehyde or heptafluorobutanal was liberated *in situ* from hemiacetal **1a** or hydrate **1b**, respectively, and allowed to react with benzyl alcohol to give racemic hemiacetal **2a** or **2b**, which was converted to the corresponding sulfonate with alkane- or arene-sulfonyl chloride, triethylamine and DMAP.^{5a,8} The resulting hemiacetal derivatives were resolved by HPLC (Daicel CHIRALPAK AD or CHIRALCEL OD) to afford (+)- and (–)-**3a–d**. Alternatively, (*S*)-(+)-**3a** (79% ee[‡]) was prepared by asymmetric addition of benzyl alcohol to trifluoroacetaldehyde using an (*R*)-binaphthol–titanium(IV) complex⁹ followed by mesylation at 0 °C.¹⁰

With sulfonates **3a–d** in hand, we then studied C–C bond-forming reactions using various organometallic reagents. In contrast to the corresponding acetaldehyde acetals,^{3,11} **3a** did

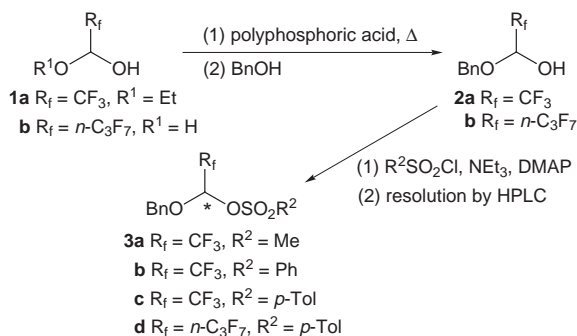
not react with $\text{Bu}_2\text{CuLi} \cdot \text{Li} / \text{BF}_3 \cdot \text{OEt}_2$. However, treatment of (*R*)-(–)-**3a** (61% ee) with AlEt_3 in toluene at –20 °C gave (–)-2-benzyloxy-1,1,1-trifluorobutane **4a** in 66% yield with 46% ee [eqn. (1) and Table 1, entry 1]. Since the absolute



configuration of ether (–)-**4a** is *S* and that of mesylate (–)-**3a** is *R*,[§] we conclude that the reaction has proceeded with inversion of configuration. This is the first observation of a stereospecific nucleophilic substitution reaction giving C–C bond formation at a CF_3 -substituted carbon with inversion of configuration, although the enantiomeric excess (ee) of **3a** was slightly lost in **4a**. This observation suggests that Lewis acid AlEt_3 induced the formation of an oxocarbenium ion intermediate, which led to racemization to some extent.³ After some trials, we were delighted to find that the use of LiAlEt_4 ¹² instead of AlEt_3 gave (*R*)-(+)-**4a** in 59% yield with 83% ee, starting from (*S*)-(+)-**3a** (83% ee).[¶] It is noteworthy that the stereochemical integrity of the substrate was completely maintained (Table 1, entry 2). Thus, the Lewis acidity of the organometallic reagent affects significantly the stereochemical course of the reaction.

To demonstrate the generality of the substitution reaction, optically active sulfonates **3a–c** were allowed to react with various organoaluminium reagents. The results are summarized in Table 1. The chirality transfer, *i.e.* the ratio of (% ee of **4**)/(% ee of **3**), is shown also. Using AlEt_3 , benzenesulfonate (*R*)-(–)-**3b**^{||} gave ether (*S*)-(–)-**4a** with 76% chirality transfer (entry 3). On the other hand, the same substrate reacted stereospecifically with LiAlEt_4 with 97% chirality transfer (entry 4). Similar results were obtained with optically active tosylate **3c** (entry 5 and 6). Reaction of (*S*)-(+)-**3c**^{||} (100% ee) with LiAlEt_4 gave (*R*)-(+)-**4a** with 98% ee. Similarly, AlMe_3 , AlBu^n_3 , and AlBu^i_3 reacted stereospecifically with optically active tosylate **3c**, while the corresponding aluminates (LiAlMe_4 , LiAlBu^n_4 and LiAlBu^i_4) reacted with higher stereospecificity (entries 8, 10 and 12 vs. entries 7, 9 and 11). The low yield of ether **4b** may be attributed to the poor solubility of LiAlMe_4 in toluene (entry 8, Table 1).

Optically active 1-benzyloxy-2,2,3,3,4,4,4-heptafluorobutyl toluene-*p*-sulfonate **3d** derived from heptafluorobutanal also reacted with organoaluminium reagents stereospecifically (entries 12 and 13). Treatment of **3d** with AlBu^i_3 afforded optically active ether **4e** with 23% chirality transfer in low yield. In contrast, **3d** reacted with LiAlBu^i_4 with 84% chirality transfer. Although the absolute configurations of sulfonate **3d** and ether **4e** remain to be determined, the reaction may be assumed to have proceeded with inversion of configuration as in the cases of **3a–c**.



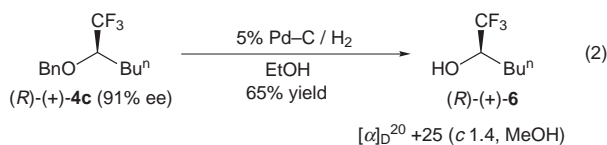
Scheme 1

Table 1 Nucleophilic substitution of optically active 1-alkoxy polyfluoroalkyl sulfonates using organoaluminium reagents

Entry	Substrate	Ee (%)	'AIR'	T/°C	t/h	Product	Yield (%)	Ee (%)	Chirality transfer (%) ^a
1	(R)-(-)- 3a^b	61	AlEt ₃	-20	0.5	(S)-(-)- 4a^d	66	46	75
2	(S)-(+)- 3a^{b,c}	83	LiAlEt ₄	0	1.5	(R)-(+)- 4a^{d,e}	59	83	100
3	(R)-(-)- 3b^f	93	AlEt ₃	-20	0.5	(S)-(-)- 4a^d	57	71	76
4	(R)-(-)- 3b^f	98	LiAlEt ₄	0	1.5	(S)-(-)- 4a^d	61	95	97
5	(S)-(+)- 3c^f	100	AlEt ₃	-20	0.5	(R)-(+)- 4a^d	75	82	82
6	(S)-(+)- 3c^{f,g}	100	LiAlEt ₄	0	1.5	(R)-(+)- 4a^{d,h}	69	98	98
7	(R)-(-)- 3c^f	91	AlMe ₃	-20	0.5	(S)-(-)- 4bⁱ	66	69	76
8	(R)-(-)- 3c^f	90	LiAlMe ₄	0-40	2.5	(S)-(-)- 4b^{i,j}	26	78	87
9	(R)-(-)- 3c^f	92	AlBu ⁿ ₃	-20	0.5	(S)-(-)- 4c^k	67	72	78
10	(S)-(+)- 3c^f	100	LiAlBu ⁿ ₄	r.t.	1.0	(R)-(+)- 4c^{k,l}	62	90	90
11	(R)-(-)- 3c^f	94	AlBu ⁿ ₃	-20	0.5	(S)-(-)- 4d^m	76	61	65
12	(S)-(+)- 3c^f	100	LiAlBu ⁿ ₄	0	1.5	(R)-(+)- 4d^{m,n}	46	93	93
13	(-)- 3d	98	AlBu ⁿ ₃	-20	0.5	(-)- 4e	17	23	23
14	(+)- 3d^o	100	LiAlBu ⁿ ₄	45	2.0	(+)- 4e^p	43	84	84

^a See text. ^b The absolute configuration was assigned on the basis of the optical rotation of (S)-(+)-**3a** prepared using an (R)-binaphthol-titanium(IV) complex (ref. 9 and 10). ^c $[\alpha]_D^{20} +46$ (c 1.0, CHCl₃). ^d The (S)-isomer prepared from (S)-3,3,3-trifluoro-1,2-epoxypropane **5** showed $[\alpha]_D^{20} -40$ (c 1.0, CHCl₃). ^e $[\alpha]_D^{20} +41$ (c 1.0, CHCl₃). ^f The absolute configuration was estimated by analogy with entries 1 and 2. ^g $[\alpha]_D^{20} +38$ (c 1.0, CHCl₃). ^h $[\alpha]_D^{20} +51$ (c 1.0, CHCl₃). ⁱ The (S)-isomer prepared from **5** showed $[\alpha]_D^{20} -15$ (c 1.0, CHCl₃). ^j $[\alpha]_D^{20} -14$ (c 1.0, CHCl₃). ^k The (S)-isomer prepared from **5** showed $[\alpha]_D^{20} -37$ (c 1.1, CHCl₃). ^l $[\alpha]_D^{20} +43$ (c 1.1, CHCl₃). ^m The (S)-isomer prepared from **5** showed $[\alpha]_D^{20} -39^\circ$ (c 1.0, CHCl₃). ⁿ $[\alpha]_D^{20} +49$ (c 1.0, CHCl₃). ^o $[\alpha]_D^{20} +33$ (c 1.1, CHCl₃). ^p $[\alpha]_D^{20} +25$ (c 1.0, CHCl₃).

The versatility of the present reaction is demonstrated by the transformation of the products to optically active 1,1,1-trifluoroalkane-2-ols [eqn. (2)]. Hydrogenolysis of benzyl ether



(R)-(+)-**4c** removed the benzyl moiety to furnish (R)-(+)-1,1,1-trifluorohexan-2-ol **6**¹³ which is a key chiral building block of antiferroelectric liquid crystalline materials.¹⁴

Notes and References

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‡ Enantiomeric excess (ee) was analyzed by HPLC with CHIRALCEL or CHIRALPAK (both available from Daicel).

§ The absolute configuration of ethers **4a-d** was assigned on the basis of the optical rotation of a corresponding authentic sample prepared from (S)-3,3,3-trifluoro-1,2-epoxypropane **5**.

¶ Typical procedure. A toluene (2.0 ml) solution of lithium tetraalkylaluminate prepared *in situ* from the corresponding alkylolithium (0.63 mmol) and trialkylaluminum (0.63 mmol) was added dropwise to a stirred solution of **3** (0.25 mmol) in toluene (2.5 ml). The reaction mixture was stirred for the indicated period and quenched with dilute HCl. The resulting mixture was extracted with Et₂O. The organic layer was washed with aq. NaCl, dried and concentrated. The residue was purified by silica gel column chromatography. All new compounds were fully characterized by IR, mass and NMR spectroscopy and elemental analysis.

|| The absolute configurations of sulfonates **3b,c** were estimated on the basis of the configurations of products **4a-d** as well as the stereochemical course of the reaction.

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