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New Expedient Route to the Stereoselective Synthesis of Fluorinated 1,3-Diol Derivatives *via* Aluminum Acetals Derived from β-Alkoxy Esters and DIBAL

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Abstract

On treating the aluminum acetal intermediates, generated *in situ* from ethyl 3-benzyloxy-2,2-difluoroalkanoates or 3-benzyloxy-4,4,4-trifluorobutanoate and diisobutylaluminum hydride at -78 ℃ for 1 h, with allylic stannanes in the presence of titanium(IV) dichloride diisopropoxide at 0 ℃ for 8 h or at -30 ℃ for 6 h, the corresponding allylated products, polyfluoro-1,3-diol derivatives, were obtained in good yields with high *anti* stereoselectivity.

Keywords: allylation; diastereoselection; diols; fluorine and compounds

Since fluorine substituents, such as monofluoro, difluoromethylene, and trifluoromethyl, introduced to organic molecules are frequently observed to exert significant effect on their biochemical properties [1], extensive efforts have continually been made to synthesize various types of fluorine-containing biologically active compounds [2]. Regioselectively fluorinated 1,3-diols of defined stereochemistry are a useful class of compounds in organic synthesis, and should be employed as building blocks for preparing fluorinated analogues of organic natural products, many of which involve a 1,3-dioxygenated framework. Therefore, development of a new access to the synthesis of such 1,3-diols and their derivatives would be of exceeding value.

In the course of our research program [3] based upon the concept that fluorinated metal acetals $R_fCH(OR)OM$, capable of essentially existing in preference to their carbonyl forms [4], would act as carbonyl equivalents in organic reactions, we have now attained the stereoselective allylation of the aluminum acetal intermediates **2**, derived from fluorinated β-alkoxy esters **1** and diisobutylaluminum hydride (DIBAL) [5], by the action of allylic stannanes and a Lewis acid leading to the *anti* isomers of 1,3-diol derivatives **3**. This communication describes the results of these reactions, along with data on the stabilities or reactivities of the intermediates **2**.

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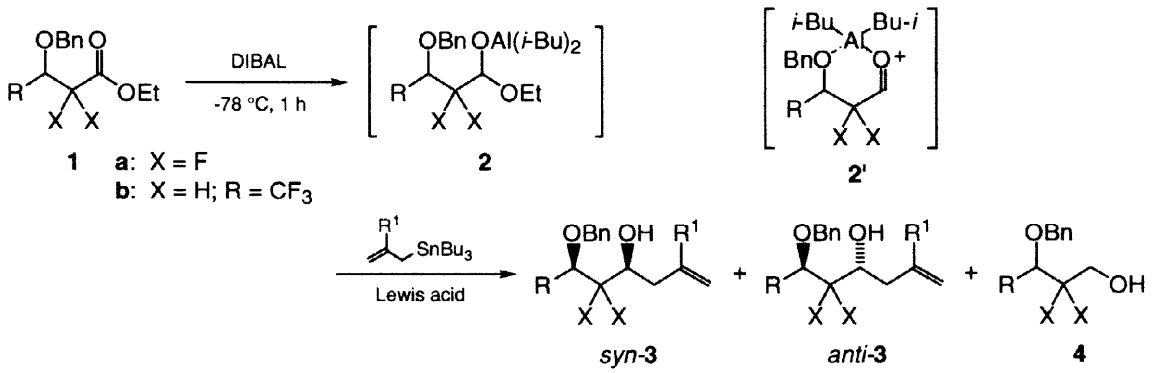
Table 1

Allylation of the aluminum acetals **2** generated *in situ* from fluorinated esters **1** and DIBAL

Entry	Ester **1** X	Ester **1** R	Stannane R^1	Lewis acid	Solvent	Temp. /°C	Time /h	Yield[a]/% of **3**	Isomer ratio[b] *syn* : *anti*	Yield[a]/% of **4**
1	F	Ph	Me	$ZnBr_2$	CH_2Cl_2	r.t.	4	71	19 : 81	3
2	F	Ph	Me	ZnI_2	CH_2Cl_2	r.t.	4	75	18 : 82	4
3	F	Ph	Me	$BF_3{\bullet}OEt_2$	CH_2Cl_2	r.t.	4	39	25 : 75	tr
4	F	Ph	Me	$TiCl_4$	CH_2Cl_2	r.t.	4	29	—	10
5	F	Ph	Me	$(i\text{-PrO})_2TiCl_2$	CH_2Cl_2	r.t.	4	71	14 : 86	7
6	F	Ph	Me	$(i\text{-PrO})_2TiCl_2$	THF	r.t.	4	9	—	tr
7	F	Ph	Me	$(i\text{-PrO})_2TiCl_2$	Toluene	r.t.	4	75	10 : 90	2
8	F	Ph	Me	$(i\text{-PrO})_2TiCl_2$	Toluene	0	4	59	7 : 93	7
9	F	Ph	Me	$(i\text{-PrO})_2TiCl_2$	Toluene	0	8	79	5 : 95	10
10	F	*p*-MeC_6H_4	Me	$(i\text{-PrO})_2TiCl_2$	Toluene	0	8	73	7 : 93	tr
11	F	*p*-$MeOC_6H_4$	Me	$(i\text{-PrO})_2TiCl_2$	Toluene	0	8	69	8 : 92	tr
12	F	*p*-ClC_6H_4	Me	$(i\text{-PrO})_2TiCl_2$	Toluene	0	8	68	7 : 93	6
13	F	*p*-FC_6H_4	Me	$(i\text{-PrO})_2TiCl_2$	Toluene	0	8	71	12 : 88	9
14	F	2-Furyl	Me	$(i\text{-PrO})_2TiCl_2$	Toluene	0	8	70	14 : 86	tr
15	F	PhCH=CH	Me	$(i\text{-PrO})_2TiCl_2$	Toluene	0	8	60	22 : 78	15
16	F	*n*-Pr	Me	$(i\text{-PrO})_2TiCl_2$	Toluene	0	8	68	47 : 53	tr
17	F	*c*-Hex	Me	$(i\text{-PrO})_2TiCl_2$	Toluene	0	8	54	46 : 54	tr
18	F	Ph	H	$(i\text{-PrO})_2TiCl_2$	Toluene	0	8	52	8 : 92	19
19	F	*p*-MeC_6H_4	H	$(i\text{-PrO})_2TiCl_2$	Toluene	0	8	59	10 : 90	19
20	F	*p*-$MeOC_6H_4$	H	$(i\text{-PrO})_2TiCl_2$	Toluene	0	8	76	5 : 95	10
21	F	*p*-FC_6H_4	H	$(i\text{-PrO})_2TiCl_2$	Toluene	0	8	57	7 : 93	6
22	F	*n*-Pr	H	$(i\text{-PrO})_2TiCl_2$	Toluene	0	8	53	40 : 60	22
23	H	CF_3	Me	$(i\text{-PrO})_2TiCl_2$	CH_2Cl_2	0	2	92	35 : 65	tr
24	H	CF_3	Me	$(i\text{-PrO})_2TiCl_2$	Toluene	0	2	92	23 : 77	tr
25	H	CF_3	Me	$(i\text{-PrO})_2TiCl_2$	Toluene	-30	6	77	7 : 93	tr
26	H	CF_3	H	$(i\text{-PrO})_2TiCl_2$	Toluene	-30	6	76	8 : 92	tr
27[c]	H	CF_3	H	$(i\text{-PrO})_2TiCl_2$	Toluene	-30	6	80	6 : 94	tr

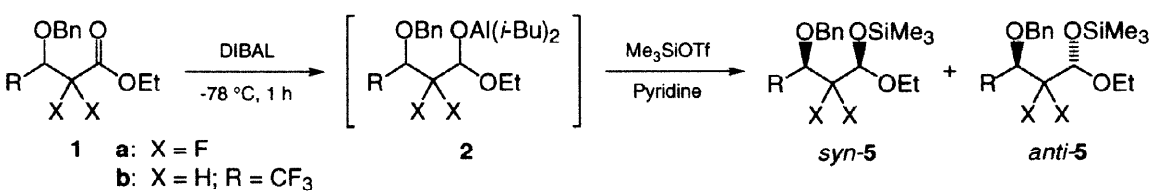
[a] The yields refer to pure products isolated by column chromatography on silica gel.
[b] Measured by ^{19}F NMR of the crude products prior to isolation. The stereochemical assignment was made on the basis of comparison of chemical shifts and couplings of **3** with those of closely related fluoro compounds reported previously [6,7].
[c] Dibutyldi(2-propenyl)stannane (1.0 equiv.) was used instead of tributyl(2-propenyl)stannane.

The starting esters **1a** and **1b** were readily accessible by the Reformatsky reaction of bromodifluoroacetate with aldehydes [8] followed by benzylation and by the benzylation of commercially available 3-hydroxy-4,4,4-trifluorobutanoate, respectively. When the ester **1a** (R = Ph) was reduced with DIBAL (1.1 equiv.) in CH_2Cl_2 at -78 °C for 1 h and subsequently treated with methallylstannane (2 equiv.) in the presence of $ZnBr_2$ (1.25 equiv.) at room temperature for 4 h, the corresponding allylated product **3a** was obtained as a 19 : 81 mixture of the *syn* and *anti* isomers in 71% yield, together with a trace amount of reduction product **4a** (Entry 1). The absence of $ZnBr_2$ decreased the yield of **3a** to 42% while it increased the yield of **4a** (39%). As regards Lewis acids other than $ZnBr_2$, ZnI_2 and $(i\text{-PrO})_2TiCl_2$ could be used effec-



tively, but BF_3•OEt_2 and $TiCl_4$ were not efficient (Entries 2-5). Toluene was a suitable solvent as well for the reaction (Entries 5-7). Eventually, the reduction of **1a** (R = Ph) with DIBAL followed by allylation in the presence of $(i\text{-PrO})_2TiCl_2$ in toluene at 0 °C for 8 h was found to provide the most satisfactory result; **3a** was obtained in 79% yield and with 95% of *anti* stereoselection (Entry 9). As summarized in Table 1, the reactions of **1a** carrying a variety of aryl substituents under the same conditions proceeded with high *anti* stereoselectivity to afford **3a** in fair to good yields (Entries 10-14 and 18-21). However, the esters **1a** having alkyl substituents underwent the reaction in an almost nonstereoselective manner (Entries 16, 17, and 22), though the reason for this stereochemical outcome is unclear.

Additionally, the present reaction protocol could nicely be applied to the ester **1b** (Entries 23-27), providing high distribution of the *anti* isomers and good yields of **3b**.



In order to estimate the stabilities or reactivities of the aluminum acetals **2**, we attempted trapping them with trimethylsilyl triflate (Me_3SiOTf) [9] under various conditions, as shown in Table 2. Thus, when *in-situ* generated **2a** (R = Ph) or **2b** was made to react with Me_3SiOTf (1.1 equiv.) and pyridine (3 equiv.) in CH_2Cl_2 at -78 °C for 3 h, the corresponding silylated acetal **5** was obtained as a diastereomeric mixture (Entries 1 and 4). Even the reaction of **2a**, which was kept at 0 °C for 1 h, with Me_3SiOTf and pyridine at 0 °C for 3 h gave rise to **5a** in 77% yield (Entry 2). The presence of $ZnBr_2$ (1.25 equiv.) led to an increase of the yield of **4a** (Entry 3). On the other hand, **2b** was entirely converted into the reduction product **4b** under similar conditions in the absence or presence of the Lewis acid (Entries 5 and 6). Consequently, the reduction products **4** are likely to arise from a Meerwein-Ponndorf-Verley-type reduction [10] of **2**. The data obtained herein suggest that the aluminum intermediates **2a** and **2b** prefer an acetal form to an aldehyde at least below 0 °C, and **2b** is more susceptible to the reduction and allylation than **2a**. This difference in the reactivity may primarily be ascribed to an electronic effect exerted by electronegative fluorine substituents; the fluorines remote from the acetal functionality can render polarization (or activation) of the C-OEt bond in **2** more feasible. The

Table 2

Trapping of the aluminum acetals **2** with trimethylsilyl triflate and pyridine

Entry	Aluminum acetal **2** X	R	Lewis acid	Temp. /℃	Time /h	Yield[a] of **5** /%	Isomer ratio[b] *syn* : *anti*	Yield[a] of **4** /%
1	F	Ph	none	-78	3	**5a** 68	78 : 22	tr
2[c]	F	Ph	none	0	3	**5a** 77	77 : 23	6
3[c]	F	Ph	$ZnBr_2$	0	3	**5a** 47	62 : 38	22
4	H	CF_3	none	-78	3	**5b** 75	81 : 19	0
5[c]	H	CF_3	none	0	3	**5b** tr	—	76
6[d]	H	CF_3	$ZnBr_2$	0	2	**5b** 0	—	74

[a] The yields are of pure products isolated by flash column chromatography on silica gel.
[b] Determined by ^{19}F NMR analysis of the crude products prior to isolation. The stereochemical assignment was tentatively made from comparison of chemical shifts and couplings of **5** with those of closely related fluoro compounds reported previously [6,7].
[c] After being stirred at 0 ℃ for 1 h, the mixture was treated with Me_3SiOTf and pyridine at 0 ℃ for a specified period.
[d] No Me_3SiOTf and pyridine were added to the reaction mixture.

above described allylation seems to occur *via* a cyclic oxocarbenium ion **2'**, which may undergo the chelation-controlled addition [11] of allylstannanes to result in the predominant formation of the *anti* isomers of the products **3**.

In short, we have demonstrated that the aluminum acetal intermediates **2**, generated *in situ* from fluorinated β-benzyloxy esters and DIBAL, participate well in the reaction with allylic stannanes in the presence of $(i\text{-PrO})_2TiCl_2$ under mild conditions to afford preferentially the *anti* isomers of fluorinated 1,3-diol derivatives **3**. The present reaction can serve as a new convenient method for the synthesis of such compounds of defined stereochemistry.

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