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Highly Stereoselective Aldol Reaction of Metal Enolates of α-Fluoropropanethioates with Aldehydes Affording *erythro*-α-Fluoro-α-methyl-β-hydroxy Alkanethioates[1]

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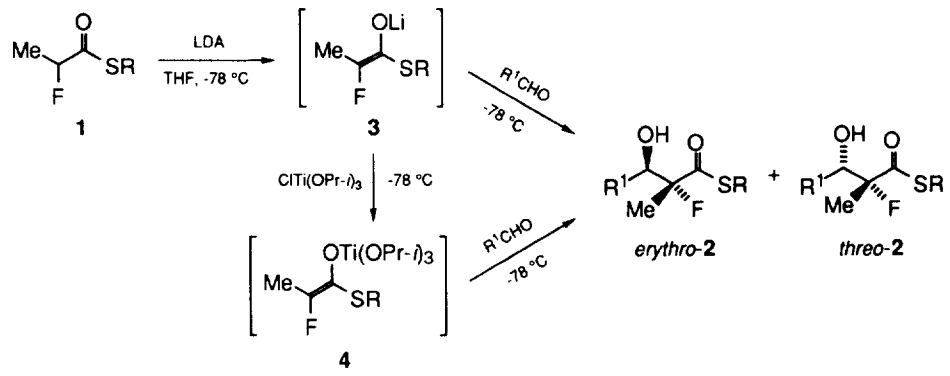
Abstract: The (*Z*)-lithium enolate of *S*-phenyl or *S*-cyclohexyl α-fluoropropanethioate reacted with aromatic aldehydes with high stereoselectivity but with aliphatic aldehydes with low levels of stereoselection. The corresponding (*Z*)-titanium enolate, generated from the lithium enolate and chlorotriisopropoxytitanium, underwent the aldol reaction in a highly stereoselective manner with aliphatic as well as aromatic aldehydes to afford *erythro*-α-fluoro-α-methyl-β-hydroxy alkanethioates in good to excellent yields.

Enolate intermediates play a central role in organic synthesis and their aldol reactions have widely been applied to the preparation of naturally occurring substances.[2] Among the various fluorine-containing enolates,[3,4] the enolates of α-fluoro carbonyl compounds are the synthetically most useful intermediates since they permit the construction of a variety of regio- and/or stereoselectively monofluorinated organic molecules, which frequently exhibit unique biological and physiological activities.[5] The generation and reactions of the enolates of fluoroacetate,[4a-g] fluoroacetamide,[4a,h] and fluoromethyl ketone[4a] have been investigated extensively, a few successful examples[4e-g] being disclosed for their stereoselective carbon-carbon bond forming reactions. In contrast, however, the enolate of α-fluoropropanoate, another important monofluoro enolate, has scarcely been explored[4d,e] despite its synthetic value. Therefore, it is of great significance to evaluate the chemistry of this enolate and to develop a promising method capable of effecting its stereocontrolled reaction.

In our continu ng studies on the chemistry and synthetic applications of fluorinated enolates,[3a-c,e,6] we have now attained, for the first time, a general and efficient method for the stereoselective aldol reaction between the metal enolates of α-fluoropropanethioates (**1**) and aldehydes to give *erythro*-α-fluoro-α-methyl-β-hydroxy alkanethioates (**2**)[7] in good to excellent yields.

Treatment of *S*-phenyl or *S*-cyclohexyl thioester **1** (R = Ph or *c*-C_6H_{11})[6] with lithium diisopropylamide (LDA) (1.1 equiv.) in tetrahydrofuran (THF) at -78 °C for 15 min led to the exclusive formation of the corresponding (*Z*)-lithium enolate **3**, which could be confirmed by the use of silylation with *tert*-butyldimethylsilyl triflate (2.1 equiv.) at -78 °C for 30 min.[6,8] It is noteworthy that the geometry of **3** is opposite to that of the lithium enolate derived from fluorine-free propanethioate and LDA.[10] This difference would be attributable to a dipolar effect exerted by the carbon-fluorine bond in **1**. Table 1 summarizes the results for the aldol reactions between the lithium enolate **3** and various aldehydes, together with those for the titanium enolate **4**.

When the enolate **3** (R = Ph) was exposed to benzaldehyde (1.0 equiv.) at -78 °C for 15 min, *S*-phenyl 2-fluoro-3-hydroxy-2-methyl-3-phenylpropanethioate (**2a**)[11,12] was obtained in 83% yield as a mixture of dia-



stereoisomers, whose *erythro* to *threo* ratio was 93 : 7 (Entry 1). Other aromatic aldehydes also underwent the aldol reaction with **3** in a highly stereoselective fashion to give preferentially the corresponding *erythro*-α-fluoro-α-methyl-β-hydroxy alkanethioates (**2**)[11,12] in excellent yields (Entries 4-7). On the other hand, the reactions of **3** with α,β-unsaturated aldehyde or aliphatic aldehydes except 2,2-dimethylpropanal under similar conditions provided us with satisfactory chemical yields of the products **2**, but with merely low levels of diastereoselection. Neither lowering the reaction temperature to -90 °C (Entry 9) nor adding *N,N,N',N'*-tetramethylethylenediamine (TMEDA) (3.3 equiv.) to the reaction mixture (Entry 11) improved the degree of stereoselectivity of the reaction as expected.

Of much interest is that the aldol reaction between **3** and 2,2-dimethylpropanal afforded *cis*-3-*tert*-butyl-2-fluoro-2-methyl-3-propanolide[11] and the desired product **2j** (*erythro*/*threo* = 50 : 50 and 67 : 33) in a ratio of 74 : 26 and 77 : 23, as shown in Entries 15 and 16, respectively. The former β-lactone was readily converted into *erythro*-**2j** quantitatively by treating with a slight excess of benzenethiol and triethylamine in THF at room temperature for 30 min. From this result and based on the observations of Danheiser and Nowick,[13] the β-lactone may be considered to result from intramolecular cyclization of an intermediary *erythro*-aldolate. Other aldehydes used did not give rise to any detectable amounts of such β-lactones in the present aldol reactions.

To overcome this defect as well as to modify the degree of stereoselectivity, a titanium enolate, *e.g.*, **4**, was applied to the aldol reaction in the following way. When the above generated lithium enolate **3** was subjected to transmetallation with chlorotriisopropoxytitanium (2.2 equiv.) at -78 °C for 1 h, followed by treatment with aldehydes (2.0 equiv.) at the same temperature for 1 h, the corresponding α-fluoro-α-methyl-β-hydroxy alkanethioates (**2**)[11,12] were obtained with much higher distributions of *erythro*-isomers than those observed for the reactions of **3**. Both aromatic (Entries 17-21) and aliphatic aldehydes (Entries 23, 26, 27, and 29) including α,β-unsaturated aldehyde (Entry 22) participated nicely in the reactions. It should be noted that the use of 2 equiv. each of the titanium reagent and aldehyde is preferred for achieving higher yield and stereoselectivity, in accordance with the findings of Siegel and Thornton.[14] The reactions of **4**, derived from **3** and 1.1 or 2.2 equiv. of the titanium reagent, with 1.0 equiv. of butanal gave substantially lower degrees of stereoselectivity (Entries 24 and 25). In the reaction with 2,2-dimethylpropanal, no β-lactone was formed and the yield of **2j** was slightly lowered (Entry 29).

The substituent R of **1** hardly affected the level of stereoselection in this aldol reaction; the lithium or titanium enolate of *S*-cyclohexyl thioester (Entries 3, 14, and 28) reacted with aldehydes with essentially the same stereoselectivity as that obtained for the corresponding enolate of *S*-phenyl thioester.

Table 1. Aldol Reactions of Metal Enolates **3** or **4** of α-Fluoropropanethioates with Aldehydes

Entry	Enolate **3** or **4** R	Metal	Aldehyde	Yield[a]/% of **2**	Isomer ratio[b] *erythro* : *threo*
1	Ph	Li	PhCHO	83 (**2a**)	93 : 7
2[c]	Ph	Li	PhCHO	80 (**2a**)	95 : 5
3	*c*-C_6H_{11}	Li	PhCHO	81 (**2a'**)	96 : 4
4	Ph	Li	*p*-MeC_6H_4CHO	86 (**2b**)	95 : 5
5	Ph	Li	*p*-$MeOC_6H_4CHO$	84 (**2c**)	91 : 9
6	Ph	Li	*p*-ClC_6H_4CHO	85 (**2d**)	92 : 8
7	Ph	Li	α-naphthaldehyde	79 (**2e**)	92 : 8
8	Ph	Li	(*E*)-MeCH=CHCHO	85 (**2f**)	69 : 31
9[d]	Ph	Li	(*E*)-MeCH=CHCHO	80 (**2f**)	73 : 27
10	Ph	Li	EtCHO	63 (**2g**)	57 : 43
11[c]	Ph	Li	EtCHO	57 (**2g**)	63 : 37
12	Ph	Li	*n*-PrCHO	59 (**2h**)	55 : 45
13	Ph	Li	*n*-HexCHO	59 (**2i**)	57 : 43
14	*c*-C_6H_{11}	Li	*n*-HexCHO	74 (**2i'**)	61 : 39
15	Ph	Li	*t*-BuCHO	68 (**2j**)[e]	87 : 13[f]
16[d]	Ph	Li	*t*-BuCHO	60 (**2j**)[e]	92 : 8[f]
17	Ph	$(i\text{-PrO})_3Ti$	PhCHO	83 (**2a**)	>97 : <3
18	Ph	$(i\text{-PrO})_3Ti$	*p*-MeC_6H_4CHO	81 (**2b**)	>97 : <3
19	Ph	$(i\text{-PrO})_3Ti$	*p*-$MeOC_6H_4CHO$	70 (**2c**)	>97 : <3
20	Ph	$(i\text{-PrO})_3Ti$	*p*-ClC_6H_4CHO	94 (**2d**)	>97 : <3
21	Ph	$(i\text{-PrO})_3Ti$	α-naphthaldehyde	80 (**2e**)	>97 : <3
22	Ph	$(i\text{-PrO})_3Ti$	(*E*)-MeCH=CHCHO	84 (**2f**)	96 : 4
23	Ph	$(i\text{-PrO})_3Ti$	EtCHO	81 (**2g**)	88 : 12
24[g]	Ph	$(i\text{-PrO})_3Ti$	*n*-PrCHO	68 (**2h**)	83 : 17
25[h]	Ph	$(i\text{-PrO})_3Ti$	*n*-PrCHO	68 (**2h**)	90 : 10
26	Ph	$(i\text{-PrO})_3Ti$	*n*-PrCHO	73 (**2h**)	92 : 8
27	Ph	$(i\text{-PrO})_3Ti$	*n*-HexCHO	75 (**2i**)	92 : 8
28	*c*-C_6H_{11}	$(i\text{-PrO})_3Ti$	*n*-HexCHO	86 (**2i'**)	93 : 7
29	Ph	$(i\text{-PrO})_3Ti$	*t*-BuCHO	51 (**2j**)	>97 : <3

a) Yields refer to analytically pure products isolated by column chromatography. b) Measured by ^{19}F NMR prior to isolation. c) TMEDA (3.3 equiv.) was added to the reaction mixture. d) Conducted at -90 °C for 30 min. e) The product **2j** and *cis*-3-*tert*-butyl-2-fluoro-2-methyl-3-propanolide were formed in a ratio of 26-23 : 74-77. The β-lactone was quantitatively transformed into *erythro*-**2j** (see text). f) Obtained after the conversion of the β-lactone into **2j**. g) 1.1 equiv. of the titanium reagent and 1.0 equiv. of aldehyde employed. h) 2.2 equiv. of the titanium reagent and 1.0 equiv. of aldehyde used.

In summary, the present aldol reactions of the metal enolates, particularly titanium enolate, of **1** with various aldehydes have been demonstrated to serve as the first efficient route to the highly stereoselective preparation of *erythro*-α-fluoro-α-methyl-β-hydroxy alkanethioates (**2**) in good yields.

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