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Highly efficient and stereoselective route to *threo*- and *erythro*-α-allylated α-fluoro-β-hydroxy esters via radical allylation reaction

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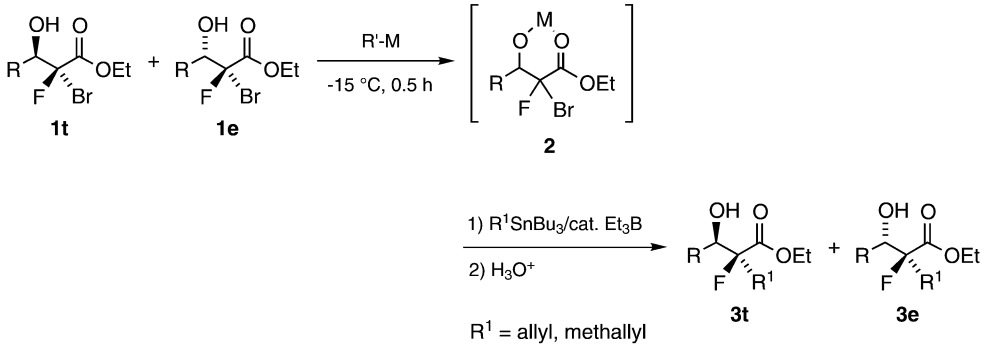
Abstract—Treatment of α-bromo-α-fluoro-β-hydroxy esters with trimethylaluminum in dichloromethane, followed by reaction with allylic stannanes and a catalytic amount of triethylborane at −15°C, gave the corresponding *threo*-α-allylated α-fluoro-β-hydroxy esters in a highly stereoselective manner. On the other hand, the reaction of the β-hydroxy esters with allylic stannanes under the influence of a catalytic amount of triethylborane in tetrahydrofuran or isopropyl alcohol at −78°C proceeded *erythro*-selectively, leading preferentially to the *erythro*-isomers of the corresponding α-allylated esters.

α-Monofluorinated β-hydroxy carboxylic acid derivatives are recognized as very important fundamental synthetic units for preparing a variety of regio- and/or stereoselectively monofluorinated natural compounds, which have attracted much attention in biological chemistry due to frequent occurrence of their specific bioactivities.[1] A general access to such α-fluoro-β-hydroxy carboxylic acid derivatives is to utilize the aldol reaction of metal enolates of fluoroacetates with aldehydes[2] or the Reformatsky reaction of bromofluoroacetate with aldehydes.[3] These reactions, however, suffer from lack of stereoselectivity. Therefore, development of a stereocontrolled means for constructing an α-fluoro-β-hydroxy carboxylate moiety will be of much synthetic value.

The recent success in the preparation of α-bromo-α-fluoro-β-hydroxy esters **1**[4] prompted us to investigate their radical reaction[5] with allylic stannane leading to α-allyl-substituted α-fluoro-β-hydroxy esters, one of the compounds of interest.

This communication discloses an efficient and discrete method for the diastereoselective synthesis of the *threo*-



Scheme 1.

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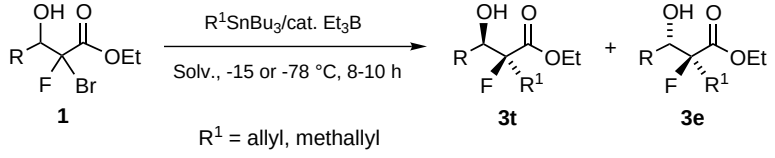
and *erythro*-isomers of α-allylated α-fluoro-β-hydroxy esters **3** based on radical allylation, of which the stereoselection is switched depending on the choice of reaction conditions (Schemes 1 and 2).

The starting α-bromo-α-fluoro-β-hydroxy esters **1** were readily prepared[4] as diastereomeric mixtures by the Reformatsky reaction of ethyl dibromofluoroacetate with aldehydes in the presence of zinc dust and diethylaluminum chloride in THF at −20°C for 1 h. First, when α-bromo-β-hydroxy ester **1a** (R = Ph) was subjected to the reaction with methallyltributylstannane in the presence of a catalytic amount of Et_3B in CH_2Cl_2 at −15°C for 6 h, the corresponding α-methallylated ester **3a** (R^1 = 2-methylpropenyl) was formed quantitatively as a diastereomeric mixture of **3at**:**3ae** = 51:49 (Table 1, entry 1). To improve the level of stereoselectivity of the reaction, we then examined the possibility of a chelation-control protocol (Scheme 1).[5a,6,7]

Thus, the ester **1a** was treated with an organometallic reagent (1.1 equiv.), such as butyllithium, diethylzinc, triisobutyl-, triethyl- or trimethylaluminum (Me_3Al), at −15°C for 0.5 h and then the resultant β-metal alkoxy ester **2a** was allowed to react with methallylstannane (2 equiv.) in the presence of catalytic Et_3B (0.1 equiv.) at that temperature for 6 h. The reaction was found to proceed in good stereoselective fashion with trialkylaluminum reagents, giving rise to the *threo*-isomer[8] of the product **3at** preferentially (entries 4–6). The use of Me_3Al gave the most satisfactory result (entry 6).[9] Out of the solvents employed, CH_2Cl_2, toluene, and THF (entries 6, 8, and 9), the best result was obtained for the reaction in CH_2Cl_2. Interestingly, the reaction in THF did not exhibit *threo*-selectivity but rather *erythro*-selectivity (entry 9). It should be noted that the reaction of the *threo*-isomer of the α-bromo ester **1at** proceeded in an entirely *threo*-selective manner, while that of the *erythro*-isomer **1ae** occurred with somewhat lower stereoselectivity, as shown in entries 10 and 11. This difference in the levels of stereoselection between the starting esters **1at** and **1ae** may be ascribed, at least partly, to the relative stability in chelation of the diastereomeric β-aluminum alkoxy esters **2a**.[7a,e,9b] Upon treating various α-bromo esters **1** successively with Me_3Al in CH_2Cl_2 at −15°C for 0.5 h and with methallyl- or allylstannane in the presence of catalytic Et_3B at the same temperature for 6 h, the corresponding α-allylated esters **3**[10] were obtained *threo*-selectively in good yields. As listed in Table 2, the esters **1** carrying a variety of substituents R, including aromatic (entries 1–8), heteroaromatic (entry 9), alkenyl (entry 10), and alkyl groups (entries 11–16), were found to be concerned nicely with the allylation reaction.[13]

The typical procedure for the *threo*-selective allylation of **1** is as follows. A 1 M hexane solution of Me_3Al (1.1 equiv.) was dropwise added to a CH_2Cl_2 solution of **1a** at −15°C under argon and the mixture was stirred for 0.5 h. To this mixture were successively added allylstannane (2.0 equiv.) and a 1 M hexane solution of Et_3B (0.1 equiv.) at −15°C. After stirring at this temperature for 6 h, a 0.1 M toluene solution of 2,6-di-*t*-butyl-*p*-cresol (0.1 equiv.) was added to the reaction mixture. After 15 min, the reaction was quenched with a 10% HCl aqueous solution, and the resulting mixture was



Scheme 2.

Table 1. Allylation of **1a** (R = Ph) with methallylstannane[a]

Entry	Ratio[b] **1at**:**1ae**	R′–M	Solvent	Yield (%)[c]	Ratio[b] **3at**:**3ae**
1	38:62	None	CH_2Cl_2	82	51:49
2	39:61	BuLi	CH_2Cl_2	24	53:47
3	39:61	Et_2Zn	CH_2Cl_2	69	51:49
4	40:60	*i*-Bu_3Al	CH_2Cl_2	56[d]	77:23
5	43:57	Et_3Al	CH_2Cl_2	67[e]	94:6
6	39:61	Me_3Al	CH_2Cl_2	83	95:5
7[f]	38:62	Me_3Al	CH_2Cl_2	79	88:12
8	38:62	Me_3Al	Toluene	80	88:12
9	38:62	Me_3Al	THF	76	30:70
10	100:0	Me_3Al	CH_2Cl_2	81	100:0
11	0:100	Me_3Al	CH_2Cl_2	79	89:11

[a] Unless otherwise noted, the reaction was conducted at −15°C for 6 h.
[b] Determined by ^{19}F NMR before isolation.
[c] Isolated yields by column chromatography.
[d] Ethyl 2-fluoro-3-hydroxy-3-phenylpropanoate (**4**) was given in 19% yield.
[e] The ester **4** was obtained in 4% yield.
[f] Carried out at −30°C for 10 h.

Table 2. *threo*-Selective allylation of **1** with allylic stannanes

Entry	R in **1**		Ratio[a] **1t**:**1e**	R[1b]	Yield (%)[c]	Ratio[a] **3t**:**3e**
1	Ph	(**a**)	38:62	M	83	95:5
2	Ph	(**a**)	38:62	A	79	96:4
3	*p*-MeC_6H_4	(**b**)	40:60	M	90	88:12
4	*p*-MeC_6H_4	(**b**)	40:60	A	73	93:7
5	*p*-$MeOC_6H_4$	(**c**)	45:55	M	85	94:6
6	*p*-$MeOC_6H_4$	(**c**)	45:55	A	73	95:5
7	*p*-ClC_6H_4	(**d**)	39:61	M	77	88:12
8	*p*-FC_6H_4	(**f**)	39:61	M	78	91:9
9	2-Furyl	(**g**)	42:58	M	64	93:7
10	MeCH=CH	(**h**)	41:59	M	74	83:17
11	*n*-Pr	(**i**)	40:60	M	86	90:10
12	*n*-Pr	(**i**)	40:60	A	72	95:5
13	*n*-Hex	(**j**)	39:61	M	94	90:10
14	*n*-Hex	(**j**)	39:61	A	86	90:10
15	*i*-Pr	(**k**)	30:70	M	75	89:11
16	*i*-Pr	(**k**)	30:70	A	80	94:6

[a] Determined by ^{19}F NMR before isolation.
[b] The abbreviations M and A for R^1 refer to the methallyl and allyl groups, respectively.
[c] Yields of analytically pure materials isolated by column chromatography.

Table 3. *erythro*-Selective allylation of **1** with allylic stannanes

Entry	R in **1**		Ratio[a] **1t**:**1e**	R[1b]	Solvent	Temp. (°C)	Time (h)	Yield (%)[c]	Ratio[a] **3t**:**3e**
1	Ph	(**a**)	38:62	M	Toluene	−15	8	83	51:49
2	Ph	(**a**)	38:62	M	CH_2Cl_2	−15	8	82	51:49
3	Ph	(**a**)	38:62	M	MeCN	−15	8	77	32:68
4	Ph	(**a**)	38:62	M	Et_2O	−15	8	80	24:76
5	Ph	(**a**)	38:62	M	DME	−15	8	88	16:84
6	Ph	(**a**)	38:62	M	THF	−15	8	85	7:93
7	Ph	(**a**)	38:62	M	THF	−78	10	95	2:98
8	Ph	(**a**)	38:62	M	*i*-PrOH	−78	10	79	3:97
9	Ph	(**a**)	38:62	A	*i*-PrOH	−78	10	80	8:92
10	*p*-MeC_6H_4	(**b**)	40:60	M	THF	−78	10	91	2:98
11	*p*-MeC_6H_4	(**b**)	40:60	A	*i*-PrOH	−78	10	85	9:91
12	*p*-$MeOC_6H_4$	(**c**)	44:56	M	THF	−78	10	93	2:98
13	*p*-$MeOC_6H_4$	(**c**)	44:56	A	*i*-PrOH	−78	10	84	9:91
14	*p*-ClC_6H_4	(**d**)	39:61	M	THF	−78	10	80	2:98
15	*p*-FC_6H_4	(**f**)	39:61	M	THF	−78	10	88	2:98
16	MeCH=CH	(**h**)	41:59	M	THF	−78	10	81	18:82
17	*n*-Pr	(**i**)	40:60	M	*i*-PrOH	−78	10	89	14:86
18	*n*-Pr	(**i**)	40:60	A	*i*-PrOH	−78	10	75	19:81
19	*i*-Pr	(**k**)	30:70	M	*i*-PrOH	−78	10	86	9:91
20	*i*-Pr	(**k**)	30:70	A	*i*-PrOH	−78	10	66	10:90

[a] Determined by ^{19}F NMR prior to isolation.
[b] The abbreviations M and A for R^1 refer to the methallyl and allyl groups, respectively.
[c] Yields of analytically pure materials isolated by column chromatography.

extracted with Et_2O and the organic layers were dried over Na_2SO_4, followed by filtration and concentration in vacuo. The residue was chromatographed on a silica gel column to give analytically pure product **3a** (Scheme 2).[10]

Meanwhile, finding that the use of THF as a solvent rendered the reaction of **2a** *erythro*-selective rather than *threo*, stimulated us to examine the solvent effect on the reaction of **1a** without Me_3Al (Scheme 2). Thus, the α-bromo ester **1a** was allowed to react directly with methallyltributylstannane under the influence of a catalytic amount of Et_3B in various solvents, like toluene, CH_2Cl_2, acetonitrile, diethyl ether, DME, THF, and 2-propanol, at −15 or −78°C for 8 or 10 h. These results are summarized in Table 3. Interestingly, the distribution of the *erythro*-isomer[8] **3ae** in the product was observed to increase markedly for the reaction in THF or 2-propanol (entries 6–8), while the reactions of **1a** in toluene, CH_2Cl_2, acetonitrile, and diethyl ether revealed nonstereoselectivity or low *erythro*-selectivity (entries 1–4). It can be noted that these findings should contribute significantly to radical chemistry as an invaluable example showing the distinct solvent effect on the stereochemical course of a radical reaction.[14] The high *erythro*-selectivity manifested by using THF and 2-

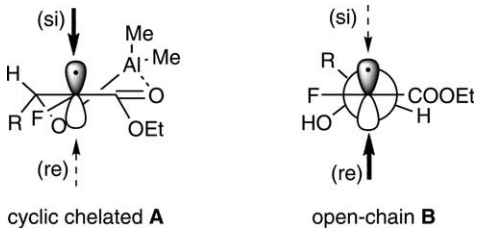


Figure 1.

propanol seems to be attributable to their potent capability of collapsing an intramolecular hydrogen bonding in **1a**, such hydrogen bonding being reported to favor the *threo*-selective course of the reaction.[14] Other α-bromo esters **1** also participated efficiently in the *erythro*-selective allylation with allylic stannanes in THF or 2-propanol to afford predominantly the corresponding *erythro*-α-allylated products **3e**[10] in good yields (entries 9–20).

The stereochemical outcomes in the present allylation reactions of **1** may be explained as follows. Thus, a β-aluminum alkoxy ester **2**, formed in situ by the reaction of **1** with Me_3Al, undergoes a bromine abstraction with the tributylstannyl radical to generate a chair-like chelated α-ester radical A (Fig. 1). This radical will be allylated more readily with allylic stannane from the less hindered *si*-face, leading preferentially to the *threo*-isomer of the product **3t**. In the case of the *erythro*-selective allylation of **1**, an open-chain α-ester radical, free from intramolecular hydrogen bonding, is generated and may be attacked by the stannane from the less hindered *re*-face of the most favored conformation B, giving rise to the *erythro*-isomer **3e**.

Although the present data, the first to show the effect of an α-fluorine substituent on the stereochemistry of the reaction, suggest that the fluorine could not have a profound effect on the stereoselectivity,[9b,15] exact evaluation of this point should await further investigations.

In summary, we have developed a convenient, effective route to the *threo*- and *erythro*-selective synthesis of α-allylated α-fluoro-β-hydroxy esters **3t** and **3e**, starting from the same α-bromo-α-fluoro-β-hydroxy esters **1** which are readily prepared from dibromofluoroacetate and aldehydes.[4] The present method should serve as a key reaction for synthesizing a number of regio- and stereoselectively monofluorinated compounds of biological interest.

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12. The acetonide from **3at**: ^{1}H NMR (300.65 MHz, $CDCl_3$, Me_4Si) δ 1.53 (s, 3H), 1.54 (s, 3H), 1.80–2.50 (m, 2H), 3.70–4.10 (m, 2H), 4.77 (d, $J=27.1$ Hz, 1H), 5.00–5.20 (m, 2H), 5.60–5.80 (m, 1H), 7.20–7.50 (m, 5H). The acetonide from **3ae**: ^{1}H NMR (300.65 MHz, $CDCl_3$, Me_4Si) δ 1.50 (s, 3H), 1.54 (s, 3H), 1.80–2.50 (m, 2H), 3.70–4.10 (m, 2H), 5.00–5.20 (m, 2H), 5.07 (d, $J=11.1$ Hz, 1H), 5.60–5.80 (m, 1H), 7.20–7.50 (m, 5H).
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