Enantio- and Diastereoselective Synthesis of *anti*-α-Bromo-α-fluoro-β-hydroxycarboxylates

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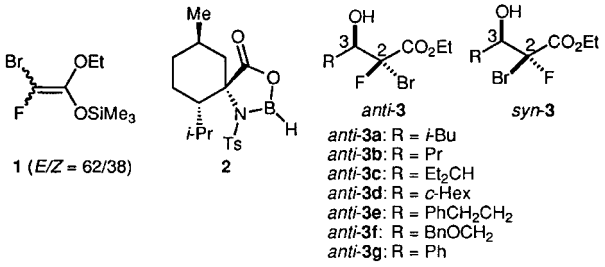
Abstract: Reaction of aldehydes with bromofluoroketene silyl acetal **1** in the presence of 20 mol% chiral Lewis acid **2** proceeds with enantio- and diastereoselectivities at -20°C to afford optically active *anti*-α-bromo-α-fluoro-β-hydroxy esters **3a-f** (up to 89:11 *anti*:*syn*, up to 93% ee).

The synthesis of chiral fluoroorganic compounds is important in the biological and medicinal chemistry fields in view of the influence of fluorine's unique properties on biological activity.[1] Fluorine, due to its high electronegativity, has a considerable electronic effect on its neighboring groups in a molecule. Thus, the introduction of fluorine into bioactive compounds frequently leads to the discovery of novel and potent biochemical tools and medicinal agents which are chiral in many cases.[2] The asymmetric Mukaiyama-aldol addition of a bromofluoroketene silyl acetal to carbonyl compounds to provide optically active α-bromo-α-fluoro-β-hydroxy esters is a valuable synthetic method since the products must be versatile intermediates for the synthesis of various useful chiral fluorinated molecules.

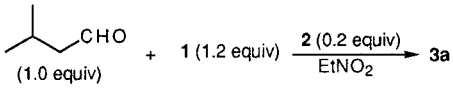
Recently, we successfully isolated bromofluoroketene ethyl trimethylsilyl acetal (**1**) and explored its application to asymmetric Mukaiyama-aldol reactions.[3] The reaction of various aldehydes with acetal **1** in the presence of Masamune's catalyst **2** at -78°C affords the corresponding optically active α-bromo-α-fluoro-β-hydroxy esters **3** with high enantioselectivities. However, the reaction is not diastereoselective (*anti/syn*). In this paper, we disclose the enantio- and diastereoselective aldol reaction of acetal **1** mediated by a chiral catalyst **2** to stereoselectively provide optically active *anti*-aldols **3**.



From the results summarized in Table 1, the *anti/syn* ratio of the aldol **3a** obtained through treatment of isovaleraldehyde with acetal **1**[4] under the influence of 20 mol% of catalyst **2**[5] was found to depend on the reaction temperature. The reaction was carried out by the addition of the aldehyde to a solution of acetal **1** and catalyst **2** in $EtNO_2$ over 3 h at the specified temperature, followed by stirring at the same temperature for 1 h prior to quenching. As with our previous work,[3] the reaction at -78°C resulted in a nearly 1:1 mixture of *anti*- and *syn*-aldols **3a** (Table 1, entry 1).[6] The reaction at -45°C also gave a similar *anti/syn* ratio (entry 2). On the contrary, *anti* diastereoselection was observed at -20 and -10°C (entries 3 and 4), and the aldol addition at -20°C provided aldol **3a** with an *anti/syn* ratio of 89/11. However, the addition of acetal **1** to a mixture of the aldehyde and catalyst **2** at -20°C completely lost all *anti* stereoselection (*anti/syn* = 39/61), and the chemical yield was also low (entry 6).

More interestingly, elevating the reaction temperature has a significant influence on the enantiofacial selection of the aldehyde. As shown in

Table 1. Effect of Reaction Temperature on the Enantiofacial Selection of Isovaleraldehyde



Entry	Temp. (°C)	Yield[a] (%)	*anti/syn*[b]	ee (*anti*)[c] (%)	ee (*syn*)[c] (%)
1[d, e]	-78	96	52/48	98 (+)	98 (+)
2[e]	-45	94	49/51	24 (-)	14 (-)
3[e]	-20	87	89/11	91 (-)	31 (-)
4[e]	-10	80	84/16	86 (-)	31 (-)
5[f]	-78	81	50/50	99 (+)	97 (+)
6[f]	-20	14	39/61	36 (+)	30 (+)

a) Isolated yields based on isovaleraldehyde; b) Based on isolated yields of *anti*- and *syn*-aldols; c) Determined by HPLC using a Daicel Chiralcel OD-H column; d) See ref. 3; e) A solution of isovaleraldehyde in $EtNO_2$ was added to a solution of **1** and **2** in $EtNO_2$ over 3 h. After stirring for an additional hour, the reaction was quenched; f) A solution of **1** in $EtNO_2$ was added to a solution of isovaleraldehyde and **2** in $EtNO_2$ over 3 h. The reaction was stirred for an additional hour prior to quenching

Table 1, entries 1-4, the aldol additions at -78°C and higher temperatures (-45 to -10°C) afforded the products, both *anti*- and *syn*-aldols **3a**, having opposite signs of optical rotation. While the *anti*-and *syn*-isomers obtained at -78°C show dextrorotation (entry 1), those at -45, -20 and -10°C are levorotatory (entries 2-4). It is very noteworthy that the reactions carried out at -78 and -20°C provides the (+)- and (-)-*anti*-α-bromo-α-fluoro-β-hydroxy esters **3a**, respectively, with significant enantioselectivities (98% ee and 91% ee). On the other hand, the *syn*-isomers obtained at -45, -20 and -10°C showed opposite optical rotation to that at -78°C (entry 1) although the degrees of enantioselectivity were modest (entries 2-4).

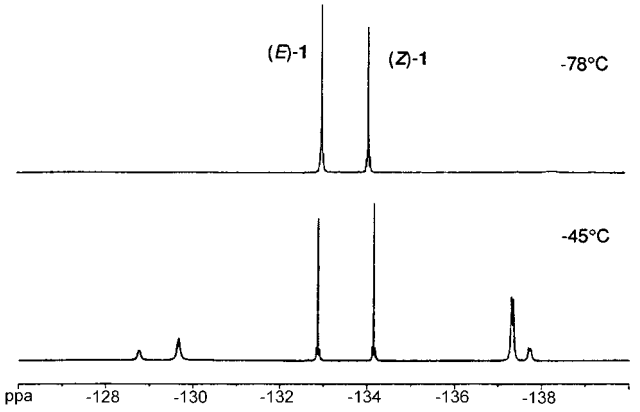
We next examined the aldol reaction of various aldehydes at -20°C under the conditions used in Table 1, entry 3. As shown in Table 2, the chemical yields were rather good. The *anti* stereoselectivity was observed except for benzaldehyde. The highest *anti/syn* ratio was obtained with butanal (89/11, entry 1). The *anti*-aldol products showed opposite signs of optical rotation to those obtained at -78°C in all cases although benzaldehyde gave a very low enantioselectivity.[7] The *anti*-aldol **3b** obtained from butanal showed the highest optical yield (93% ee, entry 1).

Table 2. Enantio- and Diastereoselective Aldol Reaction of Various Aldehydes with Acetal **1** Catalyzed by Lewis Acid **2**

Entry	Aldehyde[a] RCHO	Product	Yield[b] (%)	*anti/syn*[c]	ee (*anti*)[d] (%)
1	$CH_3CH_2CH_2CHO$	**3b**	87	89/11	93 (-)
2	$(C_2H_5)_2CHCHO$	**3c**	85	77/23	74 (-)
3	*c*-$C_6H_{11}CHO$	**3d**	90	80/20	81 (-)
4	$PhCH_2CH_2CHO$	**3e**	85	87/13	92 (-)
5	$PhCH_2OCH_2CHO$	**3f**	80	74/26	72 (-)[e]
6	PhCHO	**3g**	89	51/49	13 (2*S*,3*S*)

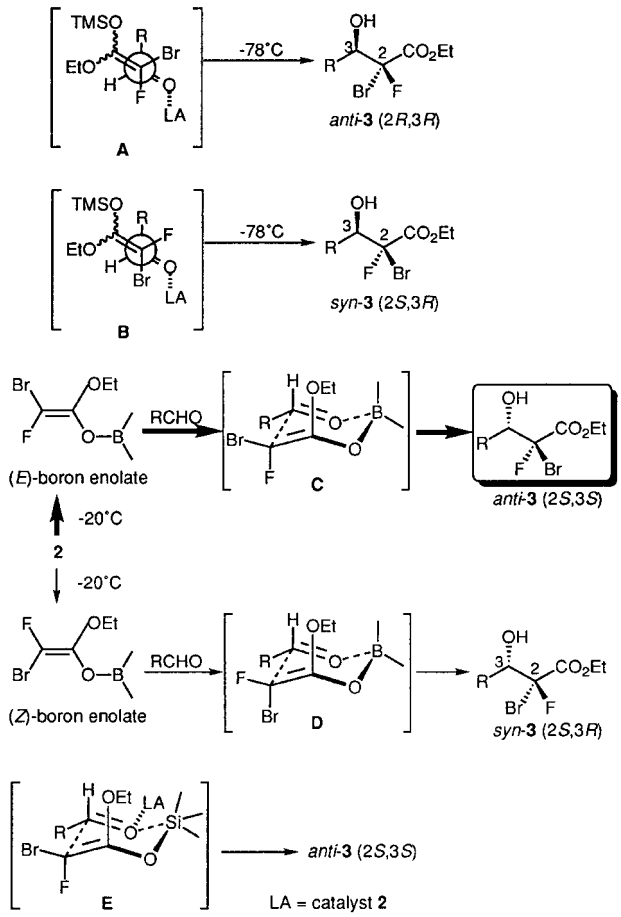
a) A solution of an aldehyde in $EtNO_2$ was added to a solution of **1** and **2** in $EtNO_2$ over 3 h at –20°C. After an additional hour at –20°C, the reaction was quenched; b) Isolated yields based on the starting aldehydes; c) Based on isolated yields of *anti*- and *syn*-aldols; d) Determined by HPLC using a Daicel Chiralcel OD-H or OB-H column. e) Determined using the corresponding acetate

The reason is not yet clear why the *anti* selectivity is obtained at -20°C and elevation of the reaction temperature causes a reversal of the enantiofacial selection, although some transition state models can be considered (Scheme 1). In the aldol reaction mediated by the catalyst **2**, the bromofluoroketene silyl acetal **1** preferentially reacts on the *si* face of the aldehydes at -78°C and the fluorine-free dimethylketene methyl trimethylsilyl acetal[5a,b] also shows the same enantiofacial selection, suggesting that the catalyst **2** plays the role of a Lewis acid and the reaction with **1** proceeds via the extended open transition states **A** and **B**. The *anti*- and *syn*-aldols are given through transition states **A** and **B**, respectively. On the contrary, the reaction with acetal **1** in the presence of the catalyst **2** at -20°C preferentially proceeds with *re* facial enantioselection.[8] We propose the cyclic chair transition states **C** and **D** leading to the reversal of the enantioselectivity when transmetallation to a boron enolate rapidly occurs.[9] As shown in the Figure, the ^{19}F NMR of a 1:1 mixture of acetal **1** and catalyst **2** in $C_2D_5NO_2$ at -78 and -20°C may suggest the formation of the boron enolate.[10] The *anti* selectivity may be caused by the predominant formation of the (*E*)-boron enolate and/or by its higher reactivity than the (*Z*)-isomer. From the (*E*)-boron enolate, the corresponding *anti*-aldol **3** should be obtained via the cyclic transition state **C**. However, a cyclic chair transition state (**E**) coordinated by the Lewis acid **2** is also a probable model leading to the *anti*-product.[11-13]



Figure

A representative experimental procedure is given by the Lewis acid **2** catalyzed reaction of isovaleraldehyde with acetal **1** (Table 1, entry 3): A 1 M THF solution of the BH_3•THF complex (200 µl, 0.2 mmol) was added dropwise to a solution of (1*S*,2*S*,5*R*)-2-isopropyl-5-methyl-1-(*N*-4'-toluenesulfonamido)cyclohexanecarboxylic acid (71 mg, 0.2 mmol) in $EtNO_2$ (3 ml) at ambient temperature under an argon atmosphere. The solution was allowed to warm to 45°C, stirred for 1 h and then cooled to -20°C. The bromofluoroketene silyl acetal **1** (*E*/*Z*: 62/38, 308 mg, 1.2 mmol) was added. A solution of isovaleraldehyde (107 µl, 1.0 mmol) in $EtNO_2$ (2 ml) was then added using a syringe pump over a 3 h period at -20°C; the resulting solution was stirred at the same temperature for an additional hour, quenched with a saturated aqueous $NaHCO_3$ solution and extracted with ether. The combined extracts were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo* after filtration. The oily residue was dissolved in a mixture of 2 N HCl (2 ml) and THF (10 ml) and stirred at ambient temperature for 1 h. The mixture was extracted with ether. The combined extracts were washed with a saturated aqueous $NaHCO_3$ solution and brine, dried with anhydrous $MgSO_4$ and filtered. After evaporation of the solvent, the residual crude product was purified by column chromatography with *n*-hexane-EtOAc as the eluent on silica gel to afford the *syn*-aldol (25 mg, 9% yield) and the *anti*-aldol (210 mg, 78% yield). The



Scheme 1. Plausible acyclic and cyclic transition states

enantioselectivities of the *syn*- and *anti*-aldols **3a** were determined to be 31% ee and 91% ee, respectively, by HPLC analysis using a chiral column (Chiralcel OD-H, Daicel Chemical Industries, Ltd.). *syn*-**3a**: a colorless oil; $[\alpha]^{26}_D$ -7.7° (*c* 0.7, $CHCl_3$); IR (neat) 3467, 2960, 1749, 1265, 1171, 1046, 666 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.92 (d, *J* = 6.5 Hz, 3H), 0.97 (d, *J* = 6.7 Hz, 3H), 1.19-1.30 (m, 1H), 1.36 (t, *J* = 7.2 Hz, 3H), 1.58-2.02 (m, 2H), 2.55-2.62 (m, 1H), 4.02-4.20 (m, 1H), 4.29-4.43 (m, 2H); ^{19}F NMR (188 MHz, $CDCl_3$, $CFCl_3$) δ -129.86 (d, *J* = 15.2 Hz, 1F); MS (FAB) *m/z* 273 [M+1$^+$], 271 [M+1$^+$]; HRMS (FAB) Calcd for $C_9H_{17}BrFO_3$ [MH$^+$] 271.0345. Found 271.0356. *anti*-**3a**: a colorless oil; $[\alpha]^{26}_D$ -26.2° (*c* 0.9, $CHCl_3$); IR (neat) 3468, 2959, 1751, 1300, 1262, 1047, 867 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.99 (d, *J* = 6.2 Hz, 3H), 1.02 (d, *J* = 6.4 Hz, 3H), 1.38 (t, *J* = 7.2 Hz, 3H), 1.48-2.25 (m, 4H), 4.12-4.32 (m, 1H), 4.39 (q, *J* = 7.2 Hz, 2H); ^{19}F NMR (188 MHz, $CDCl_3$, $CFCl_3$) δ -137.67 (d, *J* = 20.5 Hz, 1F); MS (FAB) *m/z* 273 [M+1$^+$], 271 [M+1$^+$]; HRMS (FAB) Calcd for $C_9H_{17}BrFO_3$ [MH$^+$] 271.0345. Found 271.0336.

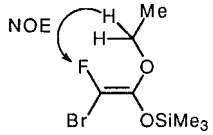
References and Notes

(1) For reviews see: (a) Welch, J. T. *Tetrahedron* **1987**, *43*, 3123. (b) Bravo, P.; Resnati, G. *Tetrahedron: Asymm.* **1990**, *1*, 661. (c) Resnati, G. *Tetrahedron* **1993**, *49*, 9385.

(2) (a) *Biomedical Aspects of Fluorine Chemistry*; Filler, R.; Kobayashi, Y. Eds.; Kodansha Ltd. and Elsevier Biomedical Press: Tokyo and Amsterdam, 1982. (b) *Biomedical Frontiers of Fluorine Chemistry*; Ojima, I.; McCarthy, J. R.; Welch, J. T. Eds.; American Chemical Society: Washington, D. C., 1996.

(3) Iseki, K.; Kuroki, Y.; Kobayashi, Y. *Tetrahedron Lett.* **1997**, *38*, 7209.

(4) The *E/Z* ratio was determined to be 62/38 by ^{19}F NMR [$CFCl_3$, $CDCl_3$; 133.1 (s, 0.62F), 134.5 (s, 0.38F)]. The minor isomer was confirmed to be the (*Z*)-acetal by the NOE between F and the methylene proton of the ethoxy group.



(*Z*)-**1**

(5) Catalyst **2** was prepared by stirring a mixture of BH_3•THF and *p*-toluenesulfonamide of the corresponding amino acid in $EtNO_2$ at 45°C for 1 h. See: (a) Parmee, E. R.; Tempkin, O.; Masamune, S. *J. Am. Chem. Soc.* **1991**, *113*, 9365. (b) Parmee, E. R.; Hong, Y.; Tempkin, O.; Masamune, S. *Tetrahedron Lett.* **1992**, *33*, 1729.

(6) Elevating the reaction temperature to -20°C and stirring for 2 h after 1 h at -78°C did not affect the *anti/syn* ratio (53/47): *anti*-**3a** [99% ee (+)]; *syn*-**3a** [99% ee (+)].

(7) The enantioselectivities of the *anti*-aldols obtained at -78°C are as follows: **3b**: 98% ee (+); **3c**: 98% ee (+); **3d**: 89% ee (+); **3e**: 98% ee (+); **3f**: 97% ee (+); **3g**: 90% ee (2*R*,3*R*). See ref. 3.

(8) In the case of the dimethylketene methyl trimethylsilyl acetal, elevating the reaction temperature to -20°C does not cause reversal of the enantiofacial selection although the degree of enantioselectivity decreases.

(9) Kuwajima, I.; Kato, M.; Mori, A. *Tetrahedron Lett.* **1980**, *21*, 4291.

(10) The ^{13}C NMR of a 1:1 mixture of dimethylketene methyl trimethylsilyl acetal and Lewis acid **2** in $C_2D_5NO_2$ at -78°C showed almost the same spectrum as that at -20°C.

(11) Mikami *et al.* proposed the silatropic ene mechanism for the asymmetric catalysis of aldol-type reactions with ketene silyl acetals. See: (a) Mikami, K.; Matsukawa, S. *J. Am. Chem. Soc.* **1994**, *116*, 4077. (b) Mikami, K.; Matsukawa, S.; Sawa, E.; Harada, A.; Koga, N. *Tetrahedron Lett.* **1997**, *38*, 1951.

(12) The aldol reaction catalyzed by a bidentate Lewis acid was reported by Maruoka *et al.* See: Ooi, T.; Takahashi, M.; Maruoka, K. *J. Am. Chem. Soc.* **1996**, *118*, 11307.

(13) Iseki, K.; Kuroki, Y.; Asada, D.; Takahashi, M.; Kishimoto, S.; Kobayashi, Y. *Tetrahedron* **1997**, *53*, 10271.