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Enantioselective Aldol Reaction with a Bromofluoroketene Silyl Acetal Catalyzed by a Chiral Lewis Acid

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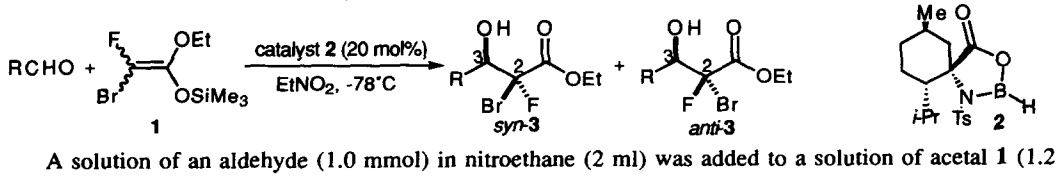
Abstract: Bromofluoroketene silyl acetal **1** was prepared in pure form. Aldol reactions of **1** with achiral aldehydes catalyzed by chiral Lewis acid **2** proceeded with high enantioselectivity to give optically active *syn*- and *anti*-α-bromo-α-fluoro-β-hydroxy esters **3a-h**, respectively (up to 99% ee).

The synthesis of chiral fluoroorganic compounds is important in biological and medicinal chemistry 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. 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] Recently, we have successfully isolated difluoroketene ethyl trimethylsilyl acetal and explored its application to asymmetric aldol reactions for the synthesis of optically active α,α-difluoro-β-hydroxy esters.[3] In this paper, we disclose for the first time the preparation of bromofluoroketene silyl acetal **1** and the catalytic enantioselective Mukaiyama-aldol reaction of the acetal **1** in the presence of chiral Lewis acid **2** to afford optically active α-bromo-α-fluoro-β-hydroxy esters **3**.[4]

In recent years, α-bromo-α-fluoro-β-hydroxy esters **3**, prepared by the Reformatsky reaction of dibromofluoroacetate, have been shown to be useful precursors for the diastereoselective synthesis of α-fluoro-β-hydroxy[5] and α-allyl-α-fluoro-β-hydroxy esters.[6] However, no attempts have been made to bring about enantioselective synthesis of chiral α-bromo-α-fluoro-β-hydroxy esters **3**. We began by preparing bromofluoroketene silyl acetal **1**. Ethyl dibromofluoroacetate was added to a mixture of chlorotrimethylsilane and activated zinc powder in THF -20°C. After 1 h at -20°C, the resulting zinc salt-containing solution of the bromofluoroketene silyl acetal **1** was diluted with *n*-pentane and filtered to remove the zinc salt, and the filtrate was concentrated *in vacuo* . After the dilution-filtration-concentration sequence was repeated once more, the residue was distilled under reduced pressure to provide **1** as a colorless oil in pure form.[7] Aldol reactions of **1** with a variety of aldehydes were carried out using Masamune's catalyst **2**.[8]



A solution of an aldehyde (1.0 mmol) in nitroethane (2 ml) was added to a solution of acetal **1** (1.2 mmol) and the catalyst (0.2 mmol) in nitroethane (3 ml) over 3 h at -78°C. After 1 h at -78°C, the reaction mixture was quenched with saturated aqueous $NaHCO_3$. After desilylation with 2 M aqueous HCl, *syn*- and *anti*-aldol products (*syn*- and *anti*-**3a-h**) were isolated by flash chromatography and the optical yields were determined by HPLC using a chiral column. The *syn*-aldol obtained from benzaldehyde (*syn*-**3a**) was shown to have the (2*S*,3*R*)-configuration by X-ray analysis of the corresponding camphanate.

Table 1. Enantioselective Aldol Reactions with Bromofluoroketene Silyl Acetal **1** Catalyzed by Lewis Acid **2**

Entry	Aldehyde (RCHO)	Product	*syn*/*anti*[a]	ee (*syn*),[b] %	ee (*anti*),[b] %	Yield,[c] %
1	C_6H_5CHO	**3a**	69:31	98 (2*S*,3*R*)[d]	90 (2*R*,3*R*)	90
2	(*E*)-C_6H_5CH=$CHCHO$	**3b**	57:43	83	83	96
3	$C_6H_5CH_2CH_2CHO$	**3c**	46:54	98	98	89
4	$C_6H_5CH_2OCH_2CHO$	**3d**	57:43	97[e]	97[e]	81
5	*c*-$C_6H_{11}CHO$	**3e**	52:48	94	89	74
6	$CH_3CH_2CH_2CHO$	**3f**	46:54	97[f]	98	90
7	$(CH_3)_2CHCH_2CHO$	**3g**	48:52	98	98	96
8	$(C_2H_5)_2CHCHO$	**3h**	54:46	99	98	70

a) Based on isolated yields of *syn*- and *anti*-aldols; b) Determined by HPLC using a Daicel Chiralcel OD-H, OB-H or AD column; c) Isolated yields based on the starting aldehydes; d) Determined by X-ray analysis of the camphanate obtained from *syn*-**3a** and (-)-camphanic chloride; e) Determined using the corresponding acetate; f) Determined using the corresponding 3,5-dinitrobenzoate.

Finally, a mixture of *syn*- and *anti*-aldols **3a** obtained from benzaldehyde using the present enantioselective aldol reaction was reduced with Bu_3SnH in the presence of Et_3Al and Et_3B in CH_2Cl_2 at -78°C according to the procedure reported by Ishihara *et al.*[5d] to afford ethyl (2*S*,3*R*)-2-fluoro-3-hydroxy-3-phenylpropanoate in 95% yield and with high diastereo- and enantioselectivities (*syn*/*anti* = 91/9,[5b,9] 98% ee). Application of the present study to synthesis of useful fluorinated bioactive compounds is now being carried out.

References and Notes

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6. Mima, K.; Hori, K.; Ishihara, T.; Yamanaka, H. *72nd National Meeting of the Chemical Society of Japan*, Tokyo, March 1997, Abstr., No. 2PA010.
7. Acetal **1** (a mixture of *E*- and *Z*-isomers): B.p. 37.0-38.5°C / 1.2 Torr; IR (neat) ν: 2964, 1703, 1255, 1149, 1060, 851 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ: 0.25 (s, 5.54H), 0.25 (s, 3.46H), 1.26 (t, *J* = 7.1 Hz, 1.85H), 1.28 (t, *J* = 7.1 Hz, 1.15H), 3.88 (q, *J* = 7.1 Hz, 1.23H), 3.95 (q, *J* = 7.1 Hz, 0.77H); ^{19}F NMR (188 MHz, $CDCl_3$) δ: 133.1 (s, 0.62F), 134.5 (s, 0.38F); MS (EI) *m*/*z*: 258 [M^+], 256 [M^+], 230, 228, 143, 141.
8. Catalyst **2** was prepared by stirring a mixture of BH_3·THF and *p*-toluenesulfonamide of the corresponding amino acid in nitroethane at 45°C for 1 h. See: a) Parmee, E.R.; Tempkin, O.; Masamune, S. *J. Am. Chem. Soc.* **1991**, *113*, 9365-9366. b) Parmee, E.R.; Hong, Y.; Tempkin, O.; Masamune, S. *Tetrahedron Lett.* **1992**, *33*, 1729-1732.
9. The ratio was determined by ^{19}F NMR [$CFCl_3$, $CDCl_3$; *syn* (δ): -203.09 (dd), *anti* (δ): -197.97 (dd)].

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