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Isolation of α,α-Difluoroketene Silyl Acetal and Its Application to Asymmetric Aldol Reactions

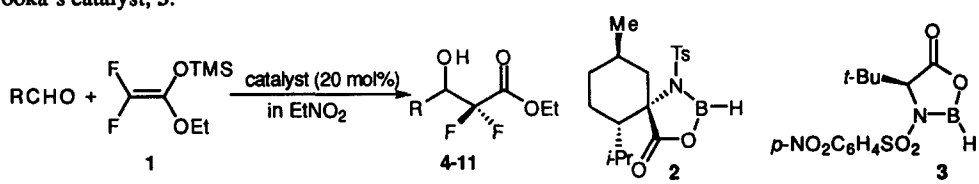
Katsuhiko Iseki,* Yoshichika Kuroki, Daisuke Asada and Yoshiro Kobayashi

MEC Laboratory, Daikin Industries, Ltd., Miyukigaoka, Tsukuba, Ibaraki 305, Japan

Abstract: Salt-free α,α-difluoroketene silyl acetal **1** was prepared in pure form. Aldol reactions of **1** with aldehydes catalyzed by catalytic amounts of chiral Lewis acids **2** and **3** proceeded with excellent enantiomeric excess to give optically active α,α-difluoro-β-hydroxy esters **4-11** (up to 98% 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 a difluoromethylene residue into bioactive peptides has led to the discovery of potent protease inhibitors mimicking the transition state for hydrolytic amide bond cleavage.[2] Optically active α,α-difluoro-β-hydroxy esters, key precursors of many useful chiral fluorinated compounds, were synthesized in a good enantioselective manner by the Reformatsky reaction of methyl bromodifluoroacetate mediated by stoichiometric amounts of chiral amino alcohols.[3] However, this transformation is less effective in respect of enantioselectivity when using substoichiometric quantities of the chiral ligands. In this paper, we describe for the first time the catalytic asymmetric Mukaiyama-aldol reaction of an α,α-difluoroketene silyl acetal using chiral Lewis acids.

Although α,α-difluoroketene silyl acetals generated *in situ* by successive treatment of α-halo-α,α-difluoroacetate with zinc metal and trialkylchlorosilane have been applied to several useful reactions including the aldol reaction,[4] no attempts have been made to bring about enantioselective reactions. Use of this impure acetal containing zinc salt is not practical for the asymmetric aldol reaction catalyzed by chiral Lewis acids since the zinc salt also acts as a Lewis acid. We began by preparing *salt-free* α,α-difluoroketene silyl acetal **1** in pure form. A solution of acetal **1** in THF obtained from ethyl bromodifluoroacetate, activated zinc powder and chlorotrimethylsilane was diluted with pentane and filtrated to remove the zinc salt. After evaporation of the solvent, the resulting oil was distilled under reduced pressure to give pure acetal **1**.[5] Aldol reactions of **1** with a variety of aldehydes were carried out using Masamune's catalyst **2**[6] and an analog of Kiyooka's catalyst, **3**.[7]



1 4-11 2 3

In the case of **2**, 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 (or -45°C). After 1 h at -78°C (or -45°C), the reaction mixture was quenched with saturated aqueous $NaHCO_3$. With catalyst **3**, acetal

1 (1.2 mmol) was added to a solution of the catalyst (0.2 mmol) and an aldehyde (1.0 mmol) at -45°C within 5 min. The reaction system was stirred at -45°C for 2 h prior to quenching with saturated aqueous $NaHCO_3$. After desilylation with 2 M aqueous HCl, aldol products **4-11** were isolated by flash chromatography and the optical yields were determined by HPLC using a chiral column. Aldol **4** was shown to have the (*R*)-configuration by conversion to the known corresponding methyl ester.[3]

Table 1. Catalytic Asymmetric Aldol Reactions of Aldehydes with α,α-Difluoroketene Silyl Acetal **1** Promoted by Lewis Acids **2** and **3**

Entry	Aldehyde RCHO	Lewis Acid (20 mol%)	Temp. (°C)	Product	Yield[a] %	ee[b] %
1	C_6H_5CHO	**2**	-78	**4**	>99	97 (*R*)
2	(*E*)-C_6H_5CH=$CHCHO$	**2**	-78	**5**	>99	96
3	$C_6H_5CH_2CH_2CHO$	**2**	-45	**6**	95	81[c]
4	$C_6H_5CH_2OCH_2CHO$	**2**	-78	**7**	94	98
5	*c*-$C_6H_{11}CHO$	**3**	-45	**8**	97	94
6	$CH_3CH_2CH_2CHO$	**3**	-45	**9**	90	94
7	$(CH_3)_2CHCH_2CHO$	**3**	-45	**10**	85	96
8	$(C_2H_5)_2CHCHO$	**3**	-45	**11**	90	95

a) Isolated yields based on the starting aldehydes; b) Determined by HPLC using a Daicel Chiralcel OD-H or AD column; c) Determined by HPLC of the corresponding acetate using a Daicel Chiralcel OB-H.

In conclusion, the aldol reaction of aldehydes with α,α-difluoroketene silyl acetal **1** mediated by Lewis acids **2** and **3** proceeded with good enantiomeric excess. Application of the present study to synthesis of useful difluorinated bioactive compounds is now being carried out.

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References and Notes

1. For reviews see: a) Welch, J.T. *Tetrahedron* **1987**, *43*, 3123-3197. b) Bravo, P.; Resnati, G. *Tetrahedron: Asymm.* **1990**, *1*, 661-692. c) Resnati, G. *Tetrahedron* **1993**, *49*, 9385-9445.
2. a) Gelb, M.H.; Svaren, J.P.; Abeles, R.H. *Biochemistry* **1985**, *24*, 1813-1817. b) Gelb, M.H. *J. Am. Chem. Soc.* **1986**, *108*, 3146-3147. c) For a review see: Kirk, K.L. Synthesis and Biochemical Applications of Fluorine-containing Peptides and Proteins. In *Fluorine-containing Amino Acids*; Kukhar', V.P.; Soloshonok, V.A. Eds.; John Wiley and Sons, Inc.: New York, 1995; pp. 343-401.
3. Braun, M.; Vonderhagen, A.; Waldmüller, D. *Liebigs Ann.* **1995**, 1447-1450.
4. a) Kitagawa, O.; Taguchi, T.; Kobayashi, Y. *Tetrahedron Lett.* **1988**, *29*, 1803-1806. b) Taguchi, T.; Kitagawa, O.; Suda, Y.; Ohkawa, S.; Hashimoto, A.; Iitaka, Y.; Kobayashi, Y. *Tetrahedron Lett.* **1988**, *29*, 5291-5294. c) Burton, D.J.; Easdon, J.C. *J. Fluorine Chem.* **1988**, *38*, 125-129. d) Kitagawa, O.; Hashimoto, A.; Kobayashi, Y.; Taguchi, T. *Chem. Lett.* **1990**, 1307-1310.
5. Acetal **1**: B.p. 51-54°C / 48 Torr; IR (neat) ν: 2967, 1271, 1256, 1144, 850 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ: 0.23 (s, 9H), 1.26 (t, *J* = 7.1 Hz, 3H), 3.87 (q, *J* = 7.1 Hz, 2H); ^{19}F NMR (188 MHz, $CDCl_3$) δ: 126.4 (d, *J* = 104.5 Hz, 1F), 127.9 (d, *J* = 104.5 Hz, 1F); MS (EI) m/z: 196 [M^+], 169, 152, 73.
6. 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.
7. Catalyst **3** was prepared by stirring a mixture of BH_3·THF and *p*-nitrobenzenesulfonamide of (*S*)-*tert*-leucine in nitroethane at 45°C for 1 h. See: a) Kiyooka, S.; Kaneko, Y.; Komura, M.; Matsuo, H.; Nakano, M. *J. Org. Chem.* **1991**, *56*, 2276-2278. b) Kiyooka, S.; Kaneko, Y.; Kume, K. *Tetrahedron Lett.* **1992**, *33*, 4927-4930.

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