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Asymmetric Aldol Addition of Aldehydes to a Difluoroketene Silyl Acetal Catalyzed by Chiral Lewis Acids

Katsuhiko Iseki,* Yoshichika Kuroki, Daisuke Asada, Mie Takahashi, Satoshi Kishimoto and Yoshiro Kobayashi

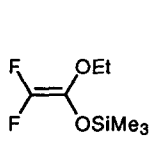
MEC Laboratory, Daikin Industries, Ltd., Miyukigaoka, Tsukuba, Ibaraki 305, Japan

Abstract: Aldol reaction of aldehydes with difluoroketene ethyl trimethylsilyl acetal (**1**) in the presence of a substoichiometric amount of chiral Lewis acid **2** or **3** provides the corresponding α,α-difluoro β-hydroxy esters **4-12** with high enantioselectivities (up to 98% ee). Reaction temperature has a great influence on the enantiofacial selection of aldehydes; the reactions of benzyloxyacetaldehyde catalyzed by Lewis acid **2** at -78 and -30°C gave the (+)- and (-)-α,α-difluoro β-hydroxy esters **7** in optical yields of 98% and 85%, respectively. © 1997 Elsevier Science Ltd.

INTRODUCTION

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] Thus, optically active α,α-difluoro β-hydroxy esters must be among the important chiral building blocks of these bioactive fluorinated compounds.

Recently, Braun *et al.* reported the Reformatsky reaction of aldehydes with methyl bromodifluoroacetate in the presence of stoichiometric amounts of chiral amino alcohols such as *N*-methylephedrine to afford the corresponding α,α-difluoro β-hydroxy esters with good enantioselectivities.[3] However, this transformation is less effective with respect to enantioselectivity when using substoichiometric quantities of the chiral ligands. We wish to describe herein that the catalytic asymmetric Mukaiyama-aldol reaction with difluoroketene ethyl trimethylsilyl acetal (**1**) can be catalyzed by chiral Lewis acids **2** and **3** in a highly enantioselective manner.[4]



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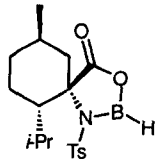

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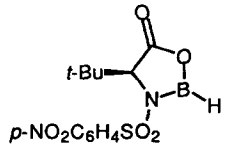

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RESULTS AND DISCUSSION

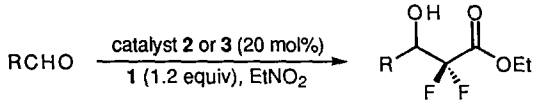
Preparation of Difluoroketene Ethyl Trimethylsilyl Acetal (1) in Pure Form. Some difluoroketene silyl acetals were reported to be generated *in situ* by successive treatment of α-halo-α,α-difluoroacetate with

activated zinc metal and trialkylchlorosilane and have been applied to the synthesis of some useful racemates including α,α-difluoro β-hydroxy esters.[5] However, no attempts using the acetals have been made to bring about enantioselective reactions. These impure difluoroketene silyl acetals containing zinc salts are not thought to be effective for the asymmetric aldol reaction catalyzed by a chiral Lewis acid because the zinc salts also act as Lewis acids. We began the present study by preparing the *salt-free* difluoroketene silyl acetal **1** in pure form.

The organozinc reagent, generated in THF by treatment of activated zinc powder with ethyl bromodifluoroacetate according to the procedure reported by Braun *et al.*,[3] was quenched with chlorotrimethylsilane at room temperature. The resulting zinc salt-containing solution of the difluoroketene silyl acetal **1** was diluted with *n*-pentane and filtered to remove the zinc salt, and the filtrate was concentrated *in vacuo* (<25°C/20-30 mmHg). After the dilution-filtration-concentration sequence was repeated two more times, the residue was distilled under reduced pressure to provide difluoroketene ethyl trimethylsilyl acetal (**1**) as a colorless oil in pure form (b.p. 51-53°C/45 mmHg).[6]

Asymmetric Aldol Reaction of Difluoroketene Ethyl Trimethylsilyl Acetal (1) with Catalytic Amounts of Chiral Lewis Acids (2 and 3). Several chiral Lewis acids, which are known to be excellent catalysts for the aldol reaction with fluorine-free ketene silyl acetals, were evaluated for their usefulness in the aldol reaction of benzaldehyde with the difluoroketene silyl acetal **1**.[7] Masamune's catalyst **2**[8] and an analog of Kiyooka's catalyst **3**[9] have been shown capable of serving as asymmetric catalysts.

Table 1. Asymmetric Aldol Reaction of Various Aldehydes with Difluoroketene Ethyl Trimethylsilyl Acetal (**1**) Catalyzed by Chiral Lewis Acids **2** and **3**



4-12

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	C_6H_5CHO	**3**	-20	(-)-**4**	96	65 (*R*)
3	(*E*)-C_6H_5CH=$CHCHO$	**2**	-78	(-)-**5**	99	96
4	(*E*)-C_6H_5CH=$CHCHO$	**3**	-45	(-)-**5**	65[c]	26
5	$C_6H_5CH_2CH_2CHO$	**2**	-78	(-)-**6**	98	76[d]
6	$C_6H_5CH_2CH_2CHO$	**3**	-45	(+)-**6**	99	70[d]
7	$C_6H_5CH_2OCH_2CHO$	**2**	-78	(+)-**7**	94	98
8	$C_6H_5CH_2OCH_2CHO$	**3**	-45	(+)-**7**	60	54
9	*c*-$C_6H_{11}CHO$	**2**	-78	(+)-**8**	87	76
10	*c*-$C_6H_{11}CHO$	**3**	-45	(+)-**8**	97	94
11	$CH_3CH_2CH_2CHO$	**2**	-78	(+)-**9**	91	97
12	$CH_3CH_2CH_2CHO$	**3**	-45	(+)-**9**	90	94
13	$CH_3(CH_2)_8CHO$	**2**	-78	(+)-**10**	93	92
14	$CH_3(CH_2)_8CHO$	**3**	-45	(+)-**10**	90	63
15	$(CH_3)_2CHCH_2CHO$	**2**	-78	(+)-**11**	85	82
16	$(CH_3)_2CHCH_2CHO$	**3**	-45	(+)-**11**	85	96
17	$(C_2H_5)_2CHCHO$	**2**	-78	(+)-**12**	81	64
18	$(C_2H_5)_2CHCHO$	**3**	-45	(+)-**12**	90	95

a) Isolated yields based on starting aldehydes; b) Determined by HPLC using a Daicel Chiralcel OD-H or AD column; c) The 1,4-adduct, ethyl 2,2-difluoro-4-formyl-3-phenylbutanoate, was obtained in 25% yield; d) Determined by HPLC of the corresponding acetate using a Daicel Chiralcel OB-H colum.

The utility of Lewis acids **2** and **3** was then assessed using a variety of aldehydes. The catalysts **2** and **3** were generated *in situ* from the corresponding sulfonamides of the chiral amino acids according to the literature procedures,[8,9] and the asymmetric aldol reaction of aromatic and aliphatic aldehydes with the acetal **1** was carried out in the presence of 20 mol% of **2** or **3**. In the case of Masamune's catalyst **2**, a solution of an aldehyde in nitroethane was added to a solution of acetal **1** (1.2 equiv) and the catalyst (20 mol%) in nitroethane over 3 h at -78°C. After stirring at -78°C for 1 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$. With catalyst **3**, acetal **1** (1.2 equiv) was added to a solution of the catalyst (20 mol%) and an aldehyde at -45°C (-20°C) in nitroethane within 5 min. The reaction system was stirred at -45°C (-20°C) for 2 h prior to quenching with saturated aqueous $NaHCO_3$. After the usual workup and desilylation with 2 N aqueous HCl, optically active α,α-difluoro β-hydroxy esters **4-12** were isolated by flash chromatography and their optical yields were determined by HPLC using chiral columns. These results are summarized in Table 1.

In most cases, the aldol reactions with catalysts **2** and **3** indeed proceeded smoothly with high chemical yields. In the reaction of (*E*)-cinnamaldehyde, catalyst **3** afforded a significant amount of the 1,4-adduct, ethyl 2,2-difluoro-4-formyl-3-phenylbutanoate, in 25% yield as well as the 1,2-adduct, ethyl (*E*)-2,2-difluoro-3-hydroxy-5-phenyl-4-pentenoate **5** (65%), although the catalyst **2** gave the desired product **5** exclusively in 99% yield (entry 4 *vs.* entry 3).

The catalyst **2** induced high enantioselection (>90% ee) for benzaldehyde, (*E*)-cinnamaldehyde, benzyloxyacetaldehyde, butanal and decanal (entries 1, 3, 7, 11 and 13). The reaction of benzaldehyde using **2** afforded ethyl 2,2-difluoro-3-hydroxy-3-phenylpropanoate **4** in 99% yield and with 97% ee (entry 1), and the major enantiomer (-)-**4** was determined to have the (*R*)-configuration by conversion to the known compound, methyl 2,2-difluoro-3-hydroxy-3-phenylpropanoate.[3]

The catalyst **3** was more effective in the enantioselection with secondary aldehydes than the catalyst **2**. The aldol reactions of cyclohexanecarboxaldehyde and 2-ethylbutanal showed greater than 90% enantiomeric excesses (entries 10 and 18).

Effects of Reaction Temperature on the Enantioface Selection of Aldehydes in the Aldol Reaction with Difluoroketene Ethyl Trimethylsilyl Acetal (1) Catalyzed by Lewis Acid 2. Interestingly, the enantiofacial selection in the aldol reaction with difluoroketene silyl acetal **1** catalyzed by Masamune's catalyst **2** was found to depend on the reaction temperature. As shown in Table 2, the lower and higher reaction temperatures afforded the products having opposite signs of optical rotation. Benzaldehyde afforded aldol (*R*)-(-)-**4** preferentially in optical yields of 97% and 81% at -78 and -60°C, respectively (entries 1 and 2). On the other hand, the reactions at -45, -30 and 0°C gave (*S*)-(-)-**4** as the major enantiomer although the degrees of enantioselectivity were modest (entries 3-5). In the case of benzyloxyacetaldehyde, ethyl (+)-4-benzyloxy-2,2-difluoro-3-hydroxybutanoate [(+)-**7**] was selectively obtained at -78 and -60°C, and the reactions at -45, -30 and 0°C gave its enantiomer (-)-**7** with good enantioselectivities (entries 6 and 7 *vs.* entries 8-10). The reactions of cyclohexanecarboxaldehyde at -78 and -45°C provided ethyl (+)- and (-)-3-cyclohexyl-2,2-difluoro-3-hydroxypropanoate (**8**), respectively, with 76% ee and 92% ee (entry 11 *vs.* entry 12). The major enantiomers obtained from butanal at -78°C, and -45 and 0°C were ethyl (+)- and (-)-2,2-difluoro-3-hydroxyhexanoate (**9**), respectively (entry 13 vs. entries 14 and 15). 3-Methylbutanal and 2-ethylbutanal also provided the opposite enantiofacial selections depending on the reaction temperature (entries 16 and 18 *vs.* entries 17 and 19). In all cases of Table 2, the enantiofacial selections at $\leq$-60°C are thought to be different from those at $\geq$-45°C, suggesting the existence of the different mechanisms dependent on the reaction temperature. The chemical yields were good to excellent.

As shown in Table 3, the aldol reaction of benzyloxyacetaldehyde with fluorine-free ketene silyl acetal **13** was catalyzed by Lewis acid **2** at -78 to 0°C to give aldol **14** in good chemical yields. However, the reversal of the enantiofacial selection was not observed, although increasing the reaction temperature decreased the optical yield. The reaction temperature-depending reversal of the enatiofacial selection, shown in Table 2, may be specific to the fluorine-containing ketene silyl acetal **1**.

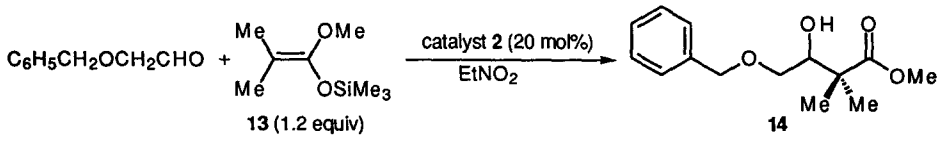
As shown in some entries in Table 2, It is notable that either enantiomer can be obtained in a synthetically useful optical yield only by selecting the reaction temperature. For example, the reaction of benzyloxyacetaldehyde with **1** was catalyzed by Lewis acid **2** at -78°C with high enantioselectivity to give the aldol (+)-**7** in 94% chemical yield and with 98% ee, while the same reaction at -30°C gave its enantiomer (-)-**7** in 88% chemical yield and with 85% ee.

Table 2. Effects of Reaction Temperature on the Enantiofacial Selection of Aldehydes in the Aldol Reaction with Difluoroketene Ethyl Trimethylsilyl Acetal (**1**) Catalyzed by Lewis Acid **2**

Entry	Aldehyde RCHO	Temp. (°C)	Product	Yield[a] %	ee[b] %
1	C_6H_5CHO	-78	(-)-**4**	99	97 (*R*)
2	C_6H_5CHO	-60	(-)-**4**	99	81 (*R*)
3	C_6H_5CHO	-45	(+)-**4**	94	33 (*S*)
4	C_6H_5CHO	-30	(+)-**4**	97	37 (*S*)
5	C_6H_5CHO	0	(+)-**4**	80	32 (*S*)
6	$C_6H_5CH_2OCH_2CHO$	-78	(+)-**7**	94	98
7	$C_6H_5CH_2OCH_2CHO$	-60	(+)-**7**	88	32
8	$C_6H_5CH_2OCH_2CHO$	-45	(-)-**7**	92	81
9	$C_6H_5CH_2OCH_2CHO$	-30	(-)-**7**	88	85
10	$C_6H_5CH_2OCH_2CHO$	0	(-)-**7**	80	81
11	*c*-$C_6H_{11}CHO$	-78	(+)-**8**	87	76
12	*c*-$C_6H_{11}CHO$	-45	(-)-**8**	90	92
13	$CH_3CH_2CH_2CHO$	-78	(+)-**9**	91	97
14	$CH_3CH_2CH_2CHO$	-45	(-)-**9**	92	79
15	$CH_3CH_2CH_2CHO$	0	(-)-**9**	79	80
16	$(CH_3)_2CHCH_2CHO$	-78	(+)-**11**	85	82
17	$(CH_3)_2CHCH_2CHO$	-45	(-)-**11**	93	75
18	$(C_2H_5)_2CHCHO$	-78	(+)-**12**	81	64
19	$(C_2H_5)_2CHCHO$	-45	(-)-**12**	92	88

a) Isolated yields based on starting aldehydes; b) Determined by HPLC using a Daicel Chiralcel OD-H or AD column.

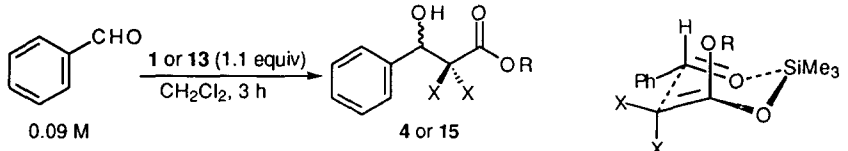
Table 3. Asymmetric Aldol Reaction of Benzyloxyacetaldehyde with Dimethylketene Methyl Trimethylsilyl Acetal (**13**) Catalyzed by Lewis Acid **2** at Various Reaction Temperatures



Entry	Temp. (°C)	Product	Yield[a] %	ee[b] %
1	-78	(+)-**14**	97	83
2	-45	(+)-**14**	88	52
3	-30	(+)-**14**	70	53
4	0	(+)-**14**	70	35

a) Isolated yields based on starting aldehydes; b) Determined by HPLC using a Daicel Chiralcel OD-H column.

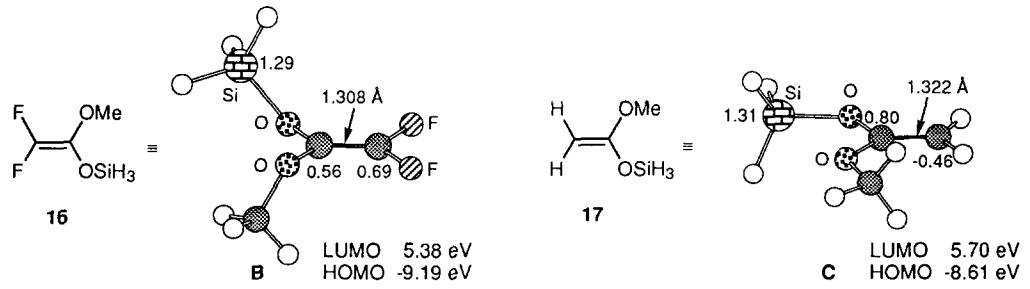
Reaction Mechanism. The difluoroketene silyl acetal **1** was found to react with benzaldehyde in the absence of a Lewis acid in dichloromethane even at -78°C to give the aldol **4** in 20% yield. On the contrary, the reaction of the aldehyde with the fluorine-free ketene silyl acetal **13** at the same temperature gave only a trace amount of ethyl 3-hydroxy-2,2-dimethyl-3-phenylpropanoate (**15**) (Scheme 1). These results show that the difluoroketene acetal **1** has higher reactivity to aldehydes than the fluorine-free acetal **13**. The aldol reaction without a Lewis acid is considered to proceed *via* a cyclic chair transition state **A** shown in Scheme 1.[10,11]



4 R = Et, X = F: 20% (-78°C), 51% (0°C), 82% (40°C)
15 R = Me, X = Me: trace (-78°C), 11% (0°C), 21% (40°C)

Scheme 1

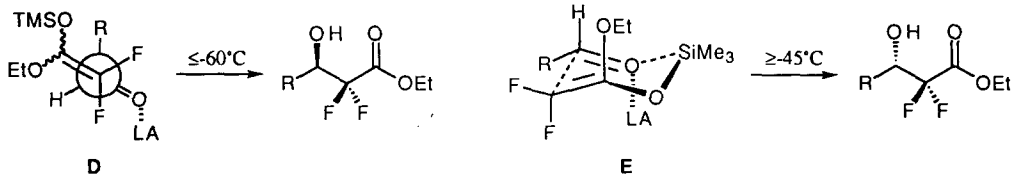
The geometries of two model acetals, difluoroketene silyl acetal **16** and fluorine-free acetal **17**, were optimized by *ab initio* molecular orbital calculation (RHF/6-31G** basis set).[12] The optimized structures **B** and **C** with minimal heats of formation were obtained from acetals **16** and **17**, respectively (Scheme 2). While the fluorine-free acetal **17** has the planar structure **C** in which the silicon-oxygen bond is on the same plane with the carbon-carbon double bond, the silicon-oxygen bond in the geometry **B** is out of the carbon-carbon double bond plane. This torsion of the silicon-oxygen bond in **B** may be ascribed to the $+I\pi$ effect of fluorine atoms. The length of the carbon-carbon double bond in **B** is shorter than that in **C**, and the difluoroketene acetal **16** has a lower LUMO level than the fluorine-free acetal **17**. The geometry **B** is considered to be more suitable for the aldol reaction without a Lewis acid than the geometry **C** because **B** bears a geometrical similarity to the ketene acetal in the transition state **A**.



Scheme 2

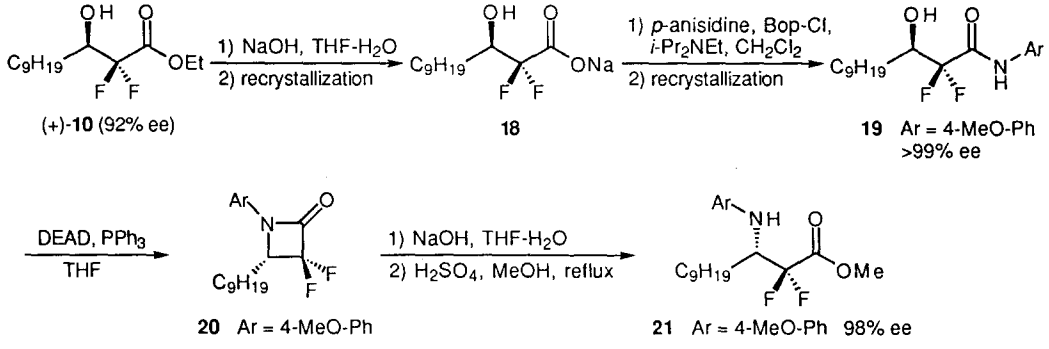
In the aldol reaction catalyzed by Lewis acid **2**, the acetal **1** reacts preferentially on the *si* face of the aldehydes at ≤-60°C and the fluorine-free dimethylketene ethyl trimethylsilyl acetal[8] also shows the same enantiofacial selectivity, suggesting that the reaction with **1** proceeds *via* the extended open transition state **D** shown in Scheme 3. On the contrary, the reaction with **1** mediated by **2** at ≥-45°C proceeds preferentially with the *re* facial enantioselection. We propose for the reversal of the enantioselectivity observed when increasing the reaction temperature that the reaction at ≥-45°C proceeds preferentially through the cyclic chair transition state coordinated by a Lewis acid (**E**).[13,14]

However, this proposal only indicates a part of the possible reaction courses for the reversal of the stereochemistry. Obviously, the understanding of the reaction mechanism at ≥-45°C must await further investigations including the direct reaction of Lewis acid **2** with the acetal **1**.



Scheme 3

Conversion of Aldol ***10*** *to an Optically Active N-Protected β-Amino α,α-Difluoro Ester* ***21***. Hydrolysis of ethyl (+)-2,2-difluoro-3-hydroxydodecanoate [(+)-**10**, 92% ee] with 1 N aqueous NaOH in THF at room temperature afforded the Na salt **18** in 80% yield. Treatment of **18** with *p*-anisidine in the presence of bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOP-Cl) and *N,N*-diisopropylethylamine (Hünig's base) in CH_2Cl_2 at room temperature for 41 h gave the amide **19** in 78% yield and with 91% ee as determined by chiral HPLC analysis.[15,16] A single recrystallization of this material from *n*-hexane-CH_2Cl_2 afforded a 64% recovery of (+)-**19** with >99% ee. The homochiral amide **19** was converted to the β-lactam **20** in nearly quantitative yield using a Mitsunobu protocol.[15,17] Hydrolysis of the β-lactam **20** with 1 N NaOH in THF, followed by the esterification of the resulting acid in a refluxing MeOH in the presence of H_2SO_4, provided the β-amino α,α-difluoro ester (-)-**21** in 92% overall yield and with 98% ee. The optically active ester **21** is thought to be a useful synthetic intermediate for a difluorinated rhodopeptin analog which shows strong antifungal activity.[18]



Scheme 4

CONCLUSION

Aldol reaction of aldehydes with difluoroketene ethyl trimethylsilyl acetal (**1**) in the presence of a substoichiometric amount of chiral Lewis acid **2** or **3** provides the corresponding α,α-difluoro β-hydroxy esters **4-12** with high enantioselectivities (up to 98% ee). Increasing the reaction temperature in the reaction catalyzed by **2** was found to cause the dramatic reversal in enantiofacial selection; the reactions of benzyloxyacetaldehyde at -78 and -30°C give the (+)- and (-)-α,α-difluoro β-hydroxy esters **7** in optical yields of 98% and 85%, respectively.

EXPERIMENTAL

General. Reactions were run under an argon atmosphere with magnetic stirring in oven-dried glassware. Nitroethane was distilled from phosphorus pentoxide in the presence of hydroquinone immediately before use.[9b] Other solvents and reagents were used as supplied or purified. Anhydrous $MgSO_4$ and Na_2SO_4 were used as the drying agents. Silica gel 60 (Merck, 230-400 mesh) was used for column chromatography. Melting points are uncorrected. Liquid chromatographic analysis was conducted at 254 nm or 230 nm using a chiral column (Daicel Chiralcel OD-H, OB-H and AD columns). Optical rotations were measured at 589 nm using a 1.0-dm cell with a total volume of 1 ml. Infrared spectra were taken either neat or in KBr pellets. Absorption was expressed in reciprocal centimeters (cm^{-1}). ^1H NMR spectra were recorded at 200 MHz and expressed in parts per million (ppm) downfield from TMS as the internal standard (δ). ^{19}F NMR spectra were measured at 188 MHz and given in parts per million (ppm) upfield from CCl_3F as the internal standard. Coupling constants are in hertz. $CDCl_3$ served as solvent for the ^1H and ^{19}F NMR. Low- and high-resolution mass spectral analyses were performed at 70 eV electron-impact (EI). Elemental analysis was carried out at the Toray Research Center, Inc., Tokyo.

Preparation of Difluoroketene Ethyl Trimethylsilyl Acetal (1): To a suspension of activated zinc powder (16.6 g, 254 mmol) in anhydrous THF (600 ml) were added 1,2-dibromoethane (1.6 ml, 18.6 mmol) and chlorotrimethylsilane (2.0 ml, 15.8 mmol) at 40°C. This mixture was stirred at the same temperature for 15 min and then cooled to room temperature. Ethyl bromodifluoroacetate (50.0 g, 246 mmol) was added dropwise over 15 mim and the mixture was stirred for 1 h. Chlorotrimethylsilane (32.2 ml, 254 mmol) was added dropwise over 10 min to the solution of the Reformatsky reagent at room temperature. After stirring for 2 h, the reaction was diluted with pentane (1.5 l), stirred vigorously for 5 min and then filtered through a pad of Celite to remove some salts. The filtrate was concentrated *in vacuo* (<25°C/20-30 mmHg). The dilution-filtration-concentration sequence was repeated two more times, and the residue was distilled under reduced pressure to give **1** (5.8 g, 12%) as a colorless oil; bp 51-53°C/45 mmHg; IR (neat) 1271, 1256, 1144, 850; ^1H NMR 0.23 (s, 9H), 1.26 (t, J = 7.1, 3H), 3.87 (q, J = 7.1, 2H); ^{19}F NMR 126.49 (d, J = 104.7, 1F), 127.75 (d, J = 104.7, 1F); MS *m/z* 196 [M^+], 152, 117, 107, 97; HRMS Calcd for $C_7H_{14}F_2O_2Si$ [M^+] 196.073, found 196.073.

General Procedure for the Aldol Reaction Catalyzed by Lewis Acid 2: To a solution of (1*S*,2*S*,5*R*)-2-isopropyl-5-methyl-1-(*N*-4'-toluenesulfonamido)cyclohexanecarboxylic acid (71 mg, 0.20 mmol) in nitroethane (3 ml) was added dropwise a 1 M THF solution of BH_3·THF complex (200 μl, 0.2 mmol) at room temperature. The solution was allowed to warm to 45°C, stirred for 1 h and cooled to -78°C. The difluoroketene acetal **1** (236 mg, 1.2 mmol) was added. A solution of the aldehyde (1.0 mmol) in nitroethane (2 ml) was then added using a syringe pump over 3 h at -78°C, and the reaction mixture was stirred at the same temperature for an additional hour, quenched with saturated $NaHCO_3$ and extracted with ether. The combined extracts were washed with brine, dried and filtered. Concentration *in vacuo* gave an oily residue which was redissolved in 2 N HCl (2 ml) and THF (10 ml). After stirring at room temperature for 1 h, the reaction mixture was extracted with ether. The combined extracts were washed with saturated $NaHCO_3$ and brine, dried and filtered. After evaporation of the solvent, chromatography of the residue with *n*-hexane-EtOAc as the eluent gave the corresponding α,α-difluoro β-hydroxy ester.

General Procedure for the Aldol Reaction Catalyzed by Lewis Acid 3: To a solution of *p*-nitrobenzenesulfonamide of (*S*)-(-)-*tert*-leucine (69.6 mg, 0.22 mmol) in nitroethane (5 ml) was added dropwise a 1 M THF solution of BH_3·THF complex (200 μl, 0.2 mmol) at room temperature. The solution was allowed to warm to 45°C, stirred for 1 h and cooled to -45°C. After the aldehyde (1.0 mmol) and **1** (236 mg, 1.2 mmol) were added, the reaction mixture was stirred at -45°C for 2 h, quenched with saturated $NaHCO_3$ and extracted with ether. The combined extracts were washed with brine, dried and filtered.

Concentration *in vacuo* gave an oily residue which was desilylated and purified according to the procedure for the reaction with **2** to afford the corresponding α,α-difluoro β-hydroxy ester.

Ethyl (*R*)-2,2-Difluoro-3-hydroxy-3-phenylpropanoate (4). a colorless oil; $[\alpha]_D^{24}$ -13.4° (*c* 1.29, $CHCl_3$) (97% ee using **2**); IR (neat) 3494, 2987, 1759, 1320, 1097; ^1H NMR 1.29 (t, *J* = 7.0, 3H), 1.58 (brs, 1H), 4.31 (q, *J* = 7.0, 2H), 5.10-5.23 (m, 1H), 7.35-7.50 (m, 5H); ^{19}F NMR 114.47 (dd, *J* = 261.7, 7.9, 1F), 120.88 (dd, *J* = 261.7, 15.6, 1F); MS *m/z* 230 [M+], 107, 79; HRMS Calcd for $C_{11}H_{12}F_2O_3$ [M+] 230.075, found 230.075.

Ethyl (*E*)-2,2-Difluoro-3-hydroxy-5-phenyl-4-pentenoate (5): a colorless oil; $[\alpha]_D^{23}$ -1.0° (*c* 1.09, $CHCl_3$) (96% ee using **2**); IR (neat) 3468, 2986, 1759, 1099, 754; ^1H NMR 1.35 (t, *J* = 7.1, 3H), 1.61 (brs, 1H), 4.37 (q, *J* = 7.1, 2H), 4.68-4.83 (m, 1H), 6.24 (dd, *J* = 16.0, 6.7, 1H), 6.82 (d, *J* = 16.0, 1H), 7.22-7.48 (m, 5H); ^{19}F NMR 114.73 (dd, *J* = 263.6, 7.9, 1F), 121.28 (dd, *J* = 263.6, 13.7, 1F); MS *m/z* 256 [M+], 133, 115; HRMS Calcd for $C_{13}H_{14}F_2O_3$ [M+] 256.091, found 256.091.

Ethyl 2,2-Difluoro-3-hydroxy-5-phenylpentanoate (6): a colorless oil; $[\alpha]_D^{21}$ -24.1° (*c* 1.84, $CHCl_3$) (76% ee using **2**); IR (neat) 3466, 2940, 1759, 1317, 1094; ^1H NMR 1.34 (t, *J* = 7.2, 3H), 1.72-2.18 (m, 3H), 2.16-3.02 (m, 2H), 3.90-4.12 (m, 1H), 4.34 (q, *J* = 7.2, 2H), 7.15-7.37 (m, 5H); ^{19}F NMR 115.14 (dd, *J* = 266.0, 7.9, 1F), 122.56 (dd, *J* = 266.0, 13.0, 1F); MS *m/z* 258 [M+], 135, 117; HRMS Calcd for $C_{13}H_{16}F_2O_3$ [M+] 258.107, found 258.106.

Ethyl 4-Benzyloxy-2,2-difluoro-3-hydroxybutanoate (7): a colorless oil; $[\alpha]_D^{22}$ +5.6° (*c* 1.44, $CHCl_3$) (98% ee using **2**); IR (neat) 3473, 2876, 1760, 1314, 1096; ^1H NMR 1.29 (t, *J* = 7.2, 3H), 2.84 (brs, 1H), 3.73 (d, *J* = 5.9, 1H), 3.74 (d, *J* = 5.5, 1H), 4.26 (q, *J* = 7.2, 2H), 4.18-4.37 (m, 1H), 4.56 (s, 2H), 7.29-7.42 (m, 5H); ^{19}F NMR 112.83 (dd, *J* = 262.0, 8.6, 1F), 120.60 (dd, *J* = 262.0, 18.0, 1F); MS *m/z* 275 [M+1], 199, 181; HRMS (FAB) Calcd for $C_{13}H_{17}F_2O_4$ [M+H] 275.109, found 275.110.

Ethyl 3-Cyclohexyl-2,2-difluoro-3-hydroxypropanoate (8): a colorless oil; $[\alpha]_D^{24}$ +18.5° (*c* 1.63, $CHCl_3$) (94% ee using **3**); IR (neat) 3480, 2929, 1760, 1317, 1096; ^1H NMR 1.01-2.08 (m, 12H), 1.37 (t, *J* = 7.1, 3H), 3.71-3.91 (m, 1H), 4.36 (q, *J* = 7.1, 2H); ^{19}F NMR 111.98 (dd, *J* = 263.0, 8.1, 1F), 120.75 (dd, *J* = 263.0, 17.7, 1F); MS *m/z* 236 [M+], 113, 95; HRMS Calcd for $C_{11}H_{18}F_2O_3$ [M+] 236.122, found 236.121.

Ethyl 2,2-Difluoro-3-hydroxyhexanoate (9): a colorless oil; $[\alpha]_D^{22}$ +23.6° (*c* 1.08, $CHCl_3$) (97% ee using **2**); IR (neat) 3451, 2965, 1760, 1315, 1060; ^1H NMR 0.97 (m, 3H), 1.37 (t, *J* = 7.2, 3H), 1.30-1.73 (m, 4H), 1.95-2.05 (m, 1H), 3.92-4.18 (m, 1H), 4.36 (q, *J* = 7.2, 2H); ^{19}F NMR 115.37 (dd, *J* = 264.0, 7.7, 1F), 123.20 (dd, *J* = 264.0, 14.9, 1F); MS *m/z* 196 [M+], 124, 73; HRMS Calcd for $C_8H_{14}F_2O_3$ [M+] 196.091, found 196.092.

Ethyl 2,2-Difluoro-3-hydroxydodecanoate (10): a colorless oil; $[\alpha]_D^{24}$ +18.1° (*c* 1.06, $CHCl_3$) (92% ee using **2**); IR (neat) 3466, 2926, 1760, 1316, 1094; ^1H NMR 0.81-0.94 (m, 3H), 1.12-2.04 (m, 17H), 1.37 (t, *J* = 7.1, 3H), 3.90-4.12 (m, 1H), 4.36 (q, *J* = 7.1, 2H); ^{19}F NMR 115.45 (dd, *J* = 264.1, 7.5, 1F), 123.01 (dd, *J* = 264.1, 15.0, 1F); MS *m/z* 280 [M+], 157, 124; HRMS Calcd for $C_{14}H_{26}F_2O_3$ [M+] 280.185, found 280.185.

Ethyl 2,2-Difluoro-3-hydroxy-5-methyhexanoate (11): a colorless oil; $[\alpha]_D^{23}$ +27.4° (*c* 1.12, $CHCl_3$) (96% ee using **3**); IR (neat) 3468, 2961, 1760, 1315, 1069; ^1H NMR 0.94 (d, *J* = 6.6, 3H), 0.99 (d, *J* = 6.6, 3H), 1.37 (t, *J* = 7.1, 3H), 1.32-1.63 (m, 2H), 1.75-2.00 (m, 1H), 1.95 (d, *J* = 7.2, 1H), 4.00-4.23 (m, 1H), 4.37 (q, *J* = 7.1, 2H); ^{19}F NMR 115.61 (dd, *J* = 264.0, 7.9, 1F), 123.12 (dd, *J* = 264.0, 14.7, 1F); MS *m/z* 210 [M+], 124, 87, 69; HRMS Calcd for $C_9H_{16}F_2O_3$ [M+] 210.107, found 210.106.

Ethyl 4-Ethyl-2,2-difluoro-3-hydroxyhexanoate (12): a colorless oil; $[\alpha]_D^{24}$ +19.8° (*c* 1.07, $CHCl_3$) (95% ee using **3**); IR (neat) 3495, 2967, 1760, 1315, 1064; ^1H NMR 0.92 (d, *J* = 7.4, 3H), 0.93 (d, *J* = 7.4, 3H), 1.20-1.80 (m, 5H), 1.37 (t, *J* = 7.2, 3H), 1.94 (brs, 1H), 3.96-4.15 (m, 1H), 4.36 (q, *J* = 7.2, 2H); ^{19}F NMR 115.44 (dd, *J* = 264.0, 8.8, 1F), 120.96 (dd, *J* = 264.0, 13.0, 1F); MS *m/z* 224 [M+], 124, 101, 83; HRMS Calcd for $C_{10}H_{18}F_2O_3$ [M+] 224.122, found 224.123.

Methyl 4-Benzyloxy-3-hydroxy-2,2-dimethylbutanoate (14): a colorless oil; $[\alpha]_D^{23}$ +2.7° (*c* 1.47, $CHCl_3$) (83% ee using **2**); IR (neat) 3452, 2948, 1732, 1454, 1142, 1090; ^1H NMR 1.21 (s, 3H), 1.22 (s, 3H), 1.63

(brs, 1H), 3.46-3.63 (m, 2H), 3.63 (s, 3H), 3.86-3.91 (m, 1H), 4.53 (s, 2H), 7.25-7.41 (m, 5H); MS *m/z* 252 [M+], 192, 131, 91; HRMS Calcd for $C_{14}H_{20}O_4$ [M+] 252.136, found 252.137.

Transformation of Aldol ***10*** *to Optically Active Ethyl N-Protected-β-amino-α,α-difluorododecanoate* ***21*** . ***N*** **-(4-Methoxyphenyl)-2,2-difluoro-3-hydroxydodecanamide (19):** Ethyl 2,2-difluoro-3-hydroxydodecanoate [(+)-**10**, 92% ee, 205 mg, 0.73 mmol] was stirred in 1 N NaOH (758 μl) and THF (1.5 ml) at room temperature. After 2.5 h, the solvents were removed *in vacuo*. The white crystalline solid that precipitated was recrystallized from *n*-hexane-EtOH to yield sodium 2,2-difluoro-3-hydroxydodecanoate (**18**, 161 mg, 80%) as colorless plates; mp 161.4-162.1°C. Bop-Cl (139 mg, 0.55 mmol) was added to a stirred solution of **18** (100 mg, 0.36 mmol), *p*-anisidine (68 mg, 0.55 mmol) and Hünig's base (71 mg, 0.55 mmol) in CH_2Cl_2 (2 ml) at room temperature. After 41 h, the reaction was extracted with CH_2Cl_2. The combined extracts were washed with 0.5 N HCl and saturated $NaHCO_3$, dried and filtered. After evaporation of the solvent, chromatography of the residue with *n*-hexane-EtOAc (6:1) as the eluent gave **19** (101 mg, 78%) as a crystalline white solid whose enantiomeric excess was determined to be 91% by HPLC using a Daicel Chiralcel OD-H column. The white solid was recrystallized from *n*-hexane-CH_2Cl_2 to afford **19** (65 mg, >99% ee) as colorless needles; mp 132.0-132.8°C; $[\alpha]_D^{23}$ +3.9° (*c* 0.45, EtOH); IR (KBr) 3312, 2920, 1681, 1543, 1249, 1086; ^{1}H NMR 0.79-0.93 (m, 3H), 1.00-1.80 (m, 17H), 3.81 (s, 3H), 4.08-4.29 (m, 1H), 6.90 (d, *J* = 9.0, 2H), 7.48 (d, *J* = 9.0, 2H), 8.00 (brs, 1H); ^{19}F NMR 113.82 (dd, *J* = 260.8, 6.0, 1F), 122.66 (dd, *J* = 260.8, 15.8, 1F); MS *m/z* 357 [M+], 149, 123; HRMS Calcd for $C_{19}H_{29}F_2NO_3$ [M+] 357.212, found 357.212; Anal. Calcd for $C_{19}H_{29}F_2NO_3$: C, 63.8; H, 8.2; N, 3.9. Found: C, 63.7; H, 8.2; N, 3.8.

3,3-Difluoro-1-(4-methoxyphenyl)-4-nonyl-2-azetidinone (20): Diethyl azodicarboxylate (DEAD, 286 μl of a 40% solution in toluene, 0.39 mmol) was added dropwise to a stirred solution of **19** (>99% ee, 63 mg, 0.18 mmol) and PPh_3 (118 mg, 0.45 mmol) at room temperature. After 40 min, the solvent was removed *in vacuo*. Chromatography of the residue with *n*-hexane-EtOAc (10:1) as the eluent gave β-lactam **20** (59 mg, 99%) as a colorless oil; IR (neat) 2927, 1777, 1515, 1253, 830; ^{1}H NMR 0.82-0.96 (m, 3H), 1.16-2.12 (m, 16H), 3.82 (s, 3H), 4.28-4.41 (m, 1H), 6.89-6.98 (m, 2H), 7.29-7.39 (m, 2H); ^{19}F NMR 114.85 (dd, *J* = 231.2, 6.6, 1F), 125.83 (d, *J* = 231.2, 1F); MS *m/z* 339 [M+], 149, 134; HRMS Calcd for $C_{19}H_{27}F_2NO_2$ [M+] 339.201, found 339.200.

Methyl 2,2-Difluoro-3-(4-methoxyphenyl)aminododecanoate (21): The β-lactam **20** (54 mg, 0.16 mmol) was stirred in 1 N NaOH (166 μl) and THF (2 ml) at room temperature. After 20 h, the solvents were removed *in vacuo*. The residue was redissolved in MeOH (5 ml), followed by the addition of concentrated H_2SO_4 (0.1 ml). After stirring under reflux for 3 h, the reaction mixture was extracted with ether. The combined extracts were washed with saturated $NaHCO_3$, dried and filtered. After evaporation of the solvent, chromatography of the residue with *n*-hexane-EtOAc (15:1) as the eluent gave **21** (54 mg, 91%) as a colorless oil whose enantiomeric excess was determined to be 98% by HPLC using a Daicel Chiralcel OD-H column; $[\alpha]_D^{22}$ -27.9° (*c* 0.66, $CHCl_3$); IR (neat) 3391, 2927, 1777, 1514, 1239, 822; ^{1}H NMR 0.80-0.92 (m, 3H), 1.09-1.92 (m, 17H), 3.71 (s, 3H), 3.74 (s, 3H), 3.78-4.05 (m, 1H), 6.55-6.80 (m, 4H); ^{19}F NMR 109.68 (dd, *J* = 256.8, 6.0, 1F), 122.15 (dd, *J* = 256.8, 19.0, 1F); MS *m/z* 371 [M+], 262; HRMS Calcd for $C_{20}H_{31}F_2NO_3$ [M+] 371.227, found 371.227.

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