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Asymmetric Catalysis of Carbonyl-Ene and Aldol Reactions with Fluoral by Chiral Binaphthol-Derived Titanium Complex

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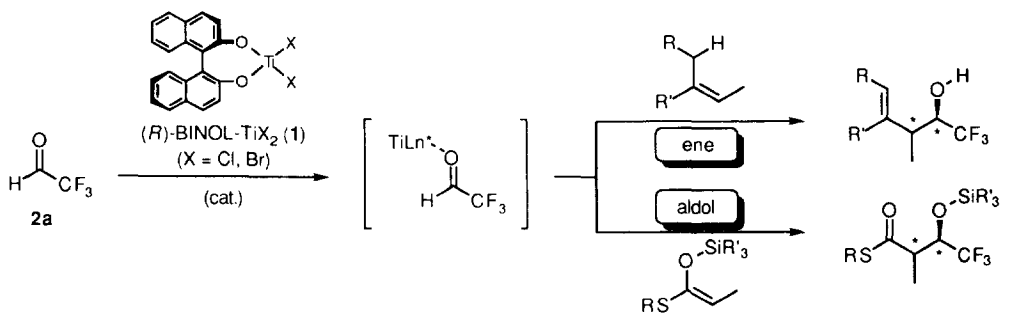
Abstract: The chiral titanium complex-catalyzed ene-type reaction and the Mukaiyama aldol reaction with fluoral are shown to serve as an efficient route to the enantioselective and diastereoselective synthesis of CF_3-substituted components of biological and synthetic importance.

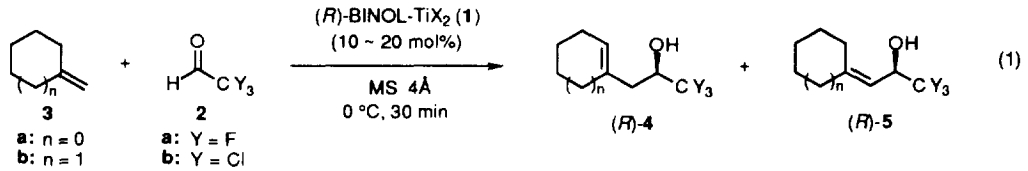
Organofluorine compounds are commonly employed in medicinal and biological chemistry.[1] Recently, chiral organofluorine compounds are also finding abiological applications in material science such as electronics and optics. For examples, fluoro threonines are reported to be highly potent anti-tumor agents.[2] Furthermore, chiral fluorinated aldol is a key component of a new type of liquid crystal, namely *anti*-ferroelectric liquid crystal molecule of tri-stable state.[3] Thus, there is current interest in developing an efficient method for the asymmetric catalytic synthesis of organofluorine compounds through carbon-carbon bond formation, which has been remained essentially unexplored thus far.[4,5] Recently, we have developed the asymmetric catalytic carbonyl-ene reaction[6] with glyoxylate, in particular, as an efficient method for asymmetric carbon-carbon bond formation by the catalysis of chiral binaphthol (BINOL)-derived titanium complexes (**1**).[7] We now wish to report herein the asymmetric catalysis of carbonyl-ene reaction and the Mukaiyama aldol reaction with fluoral (**2a**),[8,9] by the chiral BINOL-derived titanium complex (**1**) (Scheme 1).



Scheme 1

First, we examined the asymmetric catalytic fluoral-ene reactions (eq. 1, Table 1). The reaction was carried out just by simply adding an olefin (**3**) and then freshly dehydrated and distilled fluoral (**2a**) at 0 °C to the solution of the chiral titanium dihalide (**1**) prepared from (*R*)- or (*S*)-binaphthol and diisopropoxytitanium dihalide in the presence of molecular sieves (MS) 4Å as described for the glyoxylate-ene reaction.[7b,d,e] The reaction was completed within 30 min. The ene-type product, namely homoallylic alcohol (**4**) was obtained along with the

allylic alcohol (**5**) (entries 1 ~ 5). The enantiomeric purities of both products were determined to be more than 95% ee by ^{1}H NMR analysis after transformation to the (*S*)- and (*R*)-MTPA ester derivatives. The absolute configuration of the products was determined by the Mosher method.[10] The sense of asymmetric induction is, therefore, exactly the same as observed for the glyoxylate-ene reaction; the (*R*)-catalyst provides the (*R*)-alcohol products.[6,7] Thus, the catalytic ene type-reaction with fluoral provides an efficient route to the asymmetric synthesis of CF_3-containing compounds, irrespective of the solvent and halide ligand of BINOL-Ti catalyst (**1**).



(1)

Table 1. Asymmetric Catalytic Ene-type Reaction with Trihaloacetaldehydes (**2**).[a,b]

Entry	**2**	**1** (X)	**3**	solvent	%yield	**4**	(% ee)[c]	:	**5**	(% ee)[c]
1	**2a**	Cl	**3a**	CH_2Cl_2	78	62	(>95% ee)	:	38	(>95% ee)
2	**2a**	Cl	**3b**	CH_2Cl_2	93	76	(>95% ee)	:	24	(>95% ee)
3	**2a**	Br	**3b**	CH_2Cl_2	95	79	(>95% ee)	:	21	(>95% ee)
4	**2a**	Cl	**3a**	toluene	82	77	(>95% ee)	:	23	(>95% ee)
5	**2a**	Cl	**3b**	toluene	82	79	(>95% ee)	:	21	(>95% ee)
6	**2b**	Cl	**3a**	CH_2Cl_2	57	55	(26% ee)	:	45	(75% ee)
7[d]	**2b**	Br	**3a**	CH_2Cl_2	84	59	(37% ee)	:	41	(85% ee)
8	**2b**	Cl	**3b**	CH_2Cl_2	49	52	(34% ee)	:	48	(66% ee)
9[d]	**2b**	Br	**3b**	CH_2Cl_2	40	48	(45% ee)	:	52	(80% ee)
10[d]	**2b**	Cl	**3b**	toluene	35	63	(11% ee)	:	37	(66% ee)

[a] Fluoral-ene reactions were carried out with 0.1 mmol (10 mol%) of (*R*)-**1**, 1.0 mmol of **3**, and *ca.* 2.0 mmol of **2a** in the presence of MS 4Å (0.2 g). [b] Chloral-ene reactions were carried out with 0.1 mmol (10 mol%) of (*R*)-**1**, 1.5 mmol of **3**, and 1.0 mmol of **2b** in the presence of MS 4Å (0.2 g), unless otherwise marked. [c] The enantiomeric excess was determined by ^{1}H NMR analysis after transformation to the (*S*)- and (*R*)-MTPA ester derivatives. [d] 0.2 mmol (20 mol%) of (*R*)-**1** was employed.

Rather interestingly, much lower ee's were observed and more allylic alcohols were formed when chloral (**2b**) was used as the enophile (entries 6 ~ 10). Thus, the ene reactivity of trihaloacetaldehydes including acetaldehyde (**2c**) has been analyzed in terms of the balance of LUMO energy level and the electron density on the carbonyl-carbon on the basis of the MNDO, AM1, PM3, and 6-31G** calculations (Table 2).[11,12,13] Proton is used as a hypothetical Lewis acid. The refined results were obtained using the split-valence basis set with polarization functions (6-31G**).

Table 2. Computational Analysis of Trihaloacetaldehyde/H^+ Complexes.[a]

		fluoral (**2a**) / H^+	chloral (**2b**) / H^+	acetaldehyde (**2c**) / H^+
ab initio (RHF/6-31G**)	LUMO (eV)	-5.40	-4.88	-4.09
	C_1 charge	+0.61	+0.64	+0.70
PM3	LUMO (eV)	-8.64	-7.83	-7.42
	C_1 charge	+0.36	+0.39	+0.44
MNDO	LUMO (eV)	-8.55	-8.14	-7.37
	C_1 charge	+0.36	+0.42	+0.42

[a] MO calculations were run on the aldehyde (**2**) / H^+ complexes as a model of **2** / Lewis acid complexes.

Inspection of Table 2 leads us to MO analysis of the ene *vs.* cationic reactivity of trihaloacetaldehydes (**2**) (Fig. 1). The results from semi-empirical and ab-initio calculations were comparable. The frontier orbital interaction between the HOMO of the ene components and the LUMO of the carbonyl enophile is the primary interaction in ene reactions. Fluoral (**2a**) complex with the lower LUMO energy level is thus the more reactive enophile component to give mainly the homoallylic alcohols (**4**). By contrast, chloral (**2b**) complex bears the greater positive charge at the carbonyl carbon (C_1)[14] and hence is the more reactive compound in terms of the cationic, namely Friedel-Crafts-type reaction leading eventually to the allylic alcohols (**5**). Thus, the ene reactivity of aldehydes including chloral is determined in terms of the balance of LUMO energy level *vs.* electron density on the carbonyl carbons (C_1).

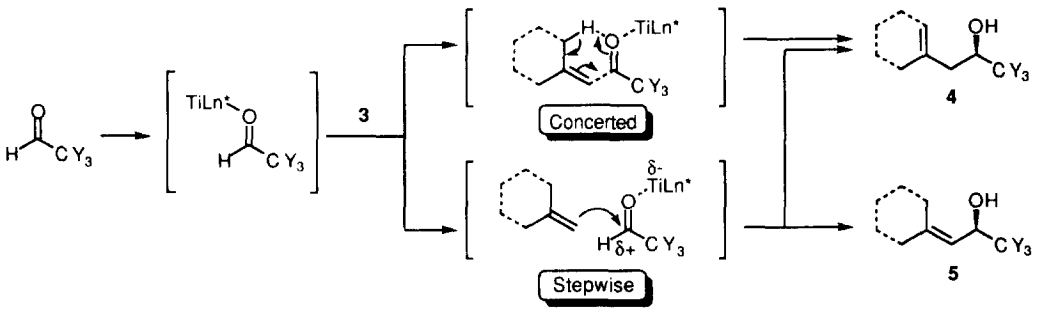
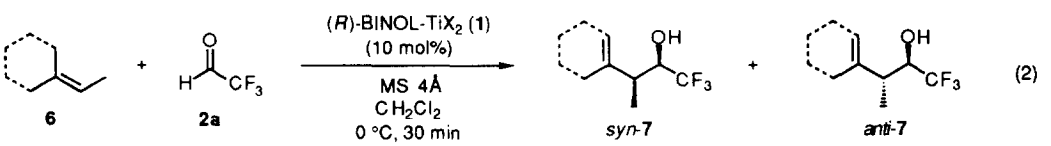


Fig. 1. Concerted *vs.* Stepwise Reaction Pathway.

We next examined the diastereo- and enantioselective catalysis of fluoral-ene reaction (eq. 2, Table 3). The reaction was carried out in the same manner described above except for the use of trisubstituted olefins (**6**). Significantly, all the fluoral-ene reactions provide the homoallylic alcohols (**7**) presumably because of the enhanced ene-reactivity by the introduction of the electron-donating methyl group,[15] along with remarkably high level of *syn*-diastereoselectivity. Thus, the catalytic fluoral-ene reaction provides an efficient route to the *syn*-diastereoselective and enantioselective synthesis of CF_3-containing compounds.



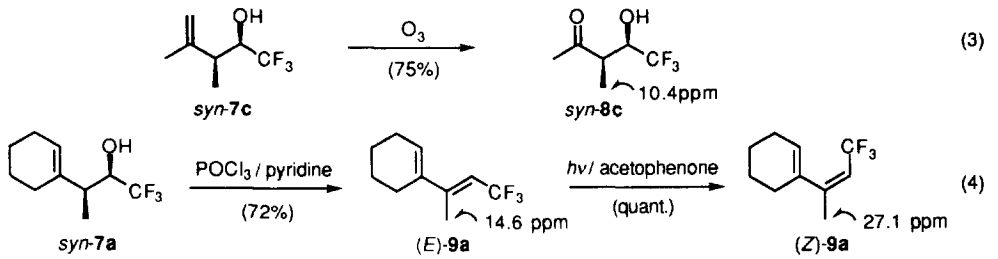
(2)

Table 3. Diastereoselective and Enantioselective Fluoral-ene Reaction.[a]

Entry	6	1 (X)	%yield	*syn*-7 (% ee)[b]	:	*anti*-7
1		Cl	94	98 (96% ee)	:	2
2	**6a**	Br	85	96 (92% ee)	:	4
3		--[c]	46	96	:	4
4		Cl	76	94 (95% ee)	:	6
5	**6b**	Br	75	98 (93% ee)	:	2
6		Cl	66	91 (78% ee)	:	9
7	**6c**	Br	74	96 (74% ee)	:	4

[a] All reactions were carried out with 0.1 mmol (10 mol%) of **1**, 1.0 mmol of **6**, and *ca.* 2.0 mmol of **2a** in the presence of MS 4Å (0.2 g), unless otherwise marked. [b] The enantiomeric excess was determined by ^1H NMR analysis after transformation to the (*S*)- and (*R*)-MTPA ester derivatives. [c] An equimolar amount of Me_2AlCl was employed.

The stereochemical assignment of the diastereomers of the fluoral-ene products deserves special comments (eqs. 3, 4). The *syn*-diastereomer (**7c**) of the fluoral-ene product with 2-methyl-2-butene (**6c**) was assigned by ^{13}C NMR analysis through ozonolysis to the aldol-type α-methyl-β-hydroxy ketone (**8c**) (eq. 3). The α-methyl carbon absorbs in the range of *syn*-diastereomers (10.4 ppm).[16] The *syn*-diastereoselectivity was further confirmed after stereospecific transformation to the dienes (**9a**) by *anti*-elimination[17] of **7a** (eq. 4). The most definitive feature is the ^{13}C NMR signals of the olefinic CH_3 carbon of the diene (**9a**) obtained by the *anti*-elimination of the fluoral-ene product (**7a**). Thus, the resultant diene (**9a**), which shows the CH_3 carbon signal at higher field (14.6 ppm) than that (27.1 ppm) of the photo-isomerized product (**9a**), can be assigned to (*E*)-diene (**9a**). Thus, the major diastereomer of the fluoral-ene product is assigned to be *syn*-isomer.



Syn-diastereoselectivity has some implications for the complexation between fluoral and the BINOL-derived titanium complex (Fig. 2). The *syn*-diastereoselectivity is analogous to that of the alkylaluminum triflate-promoted glyoxylate-ene reaction with *trans*- and *cis*-2-butene.[18] This suggests that the present fluoral-ene reaction also proceeds through the monodentate complex rather than the bidentate complex[19] leading eventually to the *anti*-diastereomers.[18] Thus the fluoral-ene reaction would proceed through the equatorial transition state (**A**), since the axial transition state (**B**) should be disfavored by the 1,3-diaxial repulsion.

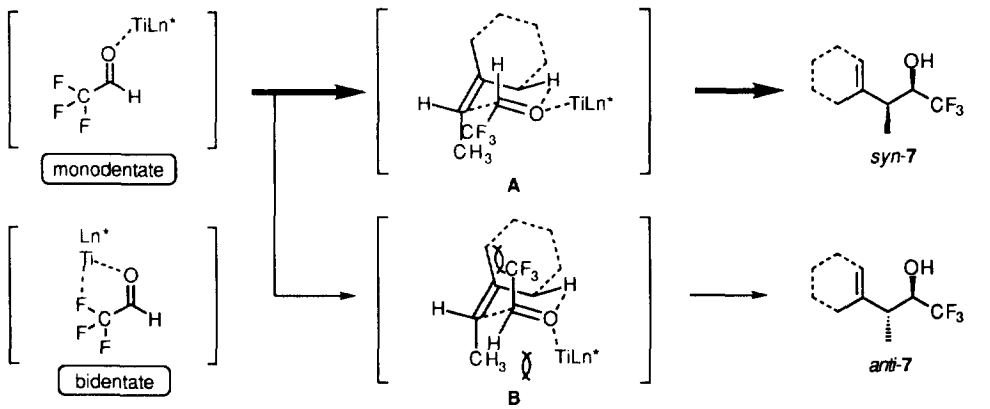
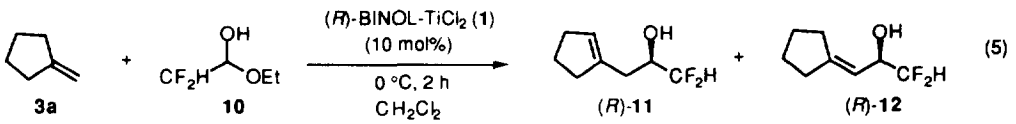


Fig. 2. Transition states of the diastereoselective fluoral-ene reaction.

The ene reaction was further examined with difluoroacetaldehyde (eq. 5). However, difluoroacetaldehyde hemiacetal (**10**) as a precursor of difluoroacetaldehyde is not readily dehydrated. Thus, we have to use the hemiacetal form (**10**) of difluoroacetaldehyde (Table 4). Though in low isolated yield (entries 1,2), we obtained the high optical yield of the ene product (**11**). The use of MS 5Å as an additive was found to increase the isolated yield (entry 3) as compared to the lower yield in the presence of MS 4Å (entry 2), presumably because of the trapping effect of ethanol by MS 5Å.



(5)

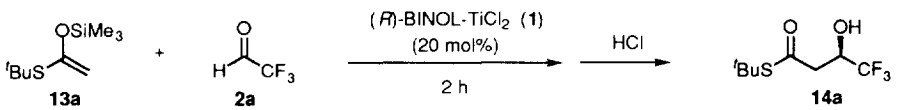
Table 4. Asymmetric Catalytic Ene-type Reaction with Difluoroacetaldehyde Hemiacetal (**10**).[a]

Entry	MS	%yield	**11**	(% ee)[b]	:	**12**	
1	--[c]	23	90	(>95% ee)	:	10	(--)
2	MS 4Å	30	93	(>95% ee)	:	7	(>95% ee)
3	MS 5Å	47	91	(>95% ee)	:	9	(--)

[a] All reactions were carried out with 0.1 mmol (10 mol%) of **1**, 1.0 mmol of **3a**, and 1.2 mmol of **10** in the presence of MS (0.2 g), unless otherwise marked. [b] The enantiomeric excess was determined by ^{1}H NMR analysis after transformation to the (*S*)- and (*R*)-MTPA ester derivatives. [c] The reaction was carried out in the absence of MS.

Next, the Mukaiyama-type aldol reactions with fluoral (**2a**) was examined. We thus attempted the asymmetric catalysis of the Mukaiyama aldol reactions with fluoral, using ketene trimethylsilyl acetal (KSA) (**13a**) which is derived from *tert*-butyl thioester (eq. 6). The reaction was carried out by adding freshly dehydrated and distilled fluoral (**2a**) and thioester-derived KSA (**13a**) to the solution of BINOL-derived chiral titanium dihalide (**1**) (Table 5). The enantiomeric purities of the aldol products (**14a**) were measured by chiral HPLC analysis. The absolute configuration of the products was determined by comparison of the optical rotation after transformation to the known ethyl ester.[20] The sense of asymmetric induction is, therefore, exactly the same as observed for the fluoral-ene reaction; the (*R*)-catalyst provides the (*R*)-alcohol products.

In sharp contrast to the results in dichloromethane (entries 3,4), the higher enantioselectivity is obtained in toluene (entries 1,2), surprisingly, at higher reaction temperature (entry 1). The remarkably high level of enantioselectivity (94% ee) was thus obtained in toluene at 0 °C, though in low chemical yield.



(6)

Table 5. Asymmetric Catalytic Mukaiyama Aldol Reaction of Fluoral (**2a**) with KSA (**13a**).[a]

Entry	solvent	temp.(°C)	% yield	% ee[b]
1	toluene	0	27	94
2		-30	40	29
3	CH_2Cl_2	0	24	33
4		-30	21	54

[a] All reactions were carried out with 0.2 mmol (20 mol%) of **1**, 1.0 mmol of **13a**, and *ca.* 2.0 mmol of **2a**. [b] The enantiomeric excess was determined by chiral HPLC analysis (Daicel CHIRALCEL OD column).

Therefore, the asymmetric catalytic Mukaiyama aldol reaction of fluoral (**2a**) with KSA (**13a**) was further examined in toluene solution (Table 6, Fig. 3). Interestingly, we have found that, even at the same temperature, the enantioselectivity of the aldol reaction is critically dependent on the turnover number (TON) of the asymmetric catalyst, namely, the yield of the aldol product / the catalyst mol% employed. Thus, the enantioselectivity decreases with increase in the TON. These results imply an another pathway for the Mukaiyama aldol reaction with fluoral, other than the asymmetric catalytic aldol process. In other words, there may be a possibility for an un-catalyzed Mukaiyama aldol process with fluoral. Indeed, the fluoral-aldol products were obtained in good yield in the absence of the catalyst even at -78 °C within 3 hours (eq. 7). These results are in sharp contrast to that with glyoxylate, which does not provide any aldol product in the absence of Lewis acid catalysis. Fluoral is so electrophilic[21] enough to undergo the Mukaiyama aldol reaction in the absence of a catalyst.

Table 6. TON *vs.* % ee in Mukaiyama Aldol Reaction.[a]

(*R*)-**1** (mol%)	TON[b]	% ee[c]
20	1.43	94
20	1.89	84
10	4.17	75
10	4.43	74

[a] All reactions were carried out with 1.0 mmol of **13a** and ca. 2.0 mmol of **2a** in toluene at 0 °C. [b] TON (turnover number): % yield of aldol product / catalyst mol% of (*R*)-**1**. [c] The enantiomeric excess was determined by chiral HPLC analysis (Daicel CHIRALCEL OD column).

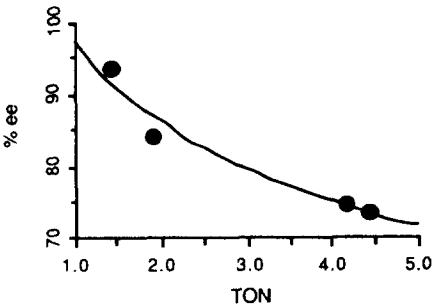
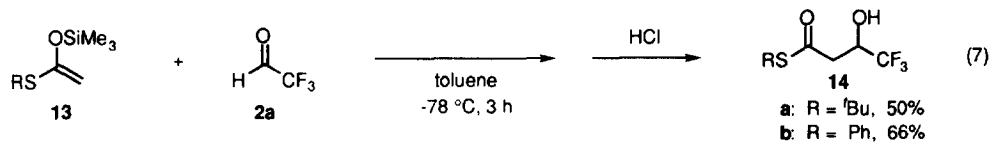
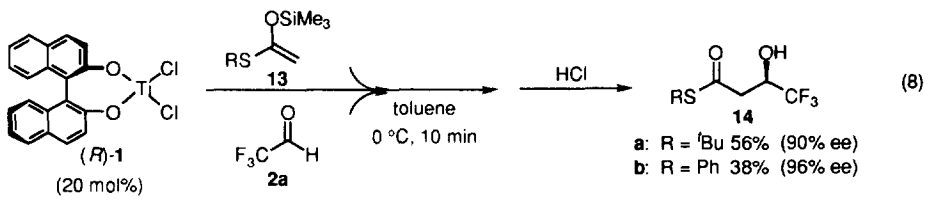


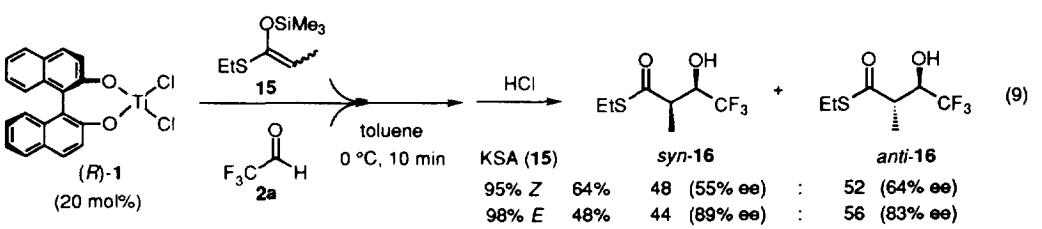
Fig. 3. TON *vs.* % ee in Mukaiyama aldol reaction



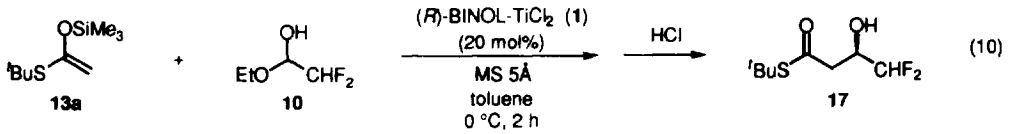
The addition procedure was therefore improved to suppress the un-catalyzed Mukaiyama aldol process; Fluoral (**2a**) and KSA (**13**) were added separately but simultaneously to the toluene solution of BINOL-derived titanium catalyst (**1**) (eq. 8). Thus, we have obtained the remarkably high enantioselectivity along with the increased chemical yield.



With the successful realization of the asymmetric catalysis, we have examined the diastereoselectivity of the Mukaiyama aldol reactions of fluoral (**2a**) with (*E*)- or (*Z*)-KSA (**15**) (eq. 9). The *syn*- and *anti*-diastereomers of the aldol products (**16**) were assigned by ^{13}C NMR analysis, according to Heathcock's report.[16] The low level of diastereoselectivity was obtained, however, along with high level of enantioselectivity, particularly in the case with (*E*)-**15**. Fortunately, *syn*- and *anti*-diastereomers (**16**) are easily separable by column chromatography.



We have further examined the aldol reaction of difluoroacetaldehyde hemiacetal (**10**) with KSA (**13a**) (eq. 10, Table 7). Though in low isolated yield, we obtained the high optical yield of the aldol product (**17**) (entry 1). The use of MS 5Å is again effective in the aldol reaction to increase the isolated yield (entry 2). Furthermore, the use of an excess amount of KSA (**13a**) is the key in obtaining the good isolated yield with the hemiacetal species of difluoroacetaldehyde (entry 3).



(10)

Table 7. Asymmetric Catalytic Mukaiyama Aldol Reaction of Difluoroacetaldehyde Hemiacetal (**10**).[a]

Entry	MS 5Å	% yield	% ee[b]
1	-[c]	20	98
2	+	30	95
3[d]	+	47	96

[a] All reactions were carried out with 0.1 mmol (20 mol%) of **1**, 0.5 mmol of KSA (**13a**), and 0.5 mmol of **10** in the presence of MS 5Å (0.5 g) in toluene at 0 °C, unless otherwise marked. [b] The enantiomeric excess was determined by chiral HPLC analysis (Daicel CHIRALCEL OD column). [c] In the absence of MS 5Å. [d] 2 eq. of KSA (**13a**) was used.

In summary, we have demonstrated here that the asymmetric catalysis of aldol and ene reactions with fluoral provides a practical access to the enantioselective and diastereoselective synthesis of fluorine-containing compounds of biological and synthetic importance.

Acknowledgment: This research was partially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Japan, the Kawakami Memorial Foundation, and Central Glass Co. Ltd.

EXPERIMENTAL SECTION

General: Boiling points are uncorrected. ^{1}H NMR and ^{13}C NMR were measured on a Varian Gemini 300 (300 MHz) spectrometers. Chemical shifts of ^{1}H NMR were expressed in parts per million downfield from tetramethylsilane as an internal standard (0 ppm) in $CDCl_3$, unless otherwise noted. Significant ^{1}H NMR data were tabulated in the following order: multiplicity (s: singlet; d: doublet; t: triplet; q: quartet; sep: septet; bs: broad singlet; br: broad; m: multiplet). Chemical shifts of ^{13}C NMR were expressed in parts per million in $CDCl_3$ as an internal standard (77.1 ppm), unless otherwise noted. IR spectra were measured on a JASCO FT/IR-5000 spectrometer. Optical rotations were measured on a JASCO DIP-140. Liquid chromatographic analyses were conducted on a Shimadzu LC-6A instrument equipped with model SPD-6A spectrometers as an ultra violet light (254 nm) and chiral column (Daicel CHIRALCEL OD). Peak area was calculated by a Shimadzu model C-R6A or C-R3A as an automatic integrator. Analytical thin layer chromatography (TLC) were performed on a glass plates and/or aluminum sheets pre-coated with silica gel (Merck Kieselgel 60 F_{254}, layer thickness 0.25 and 0.2 mm). Visualization was accomplished by UV light (254 nm), anisaldehyde, $KMnO_4$, and phosphomolybdic acid. Column chromatography was performed on Merck Kieselgel 60, employing hexane ethyl acetate mixture as eluent, unless otherwise noted. Molecular sieves (MS) 4Å (activated powder) was purchased from Aldrich Chemical Co. All experiments were carried out under nitrogen or argon atmosphere. Toluene was distilled from sodium benzophenone kethyl immediately prior to use. Dichloromethane, hexane, and pentane were freshly distilled over CaH_2.

General Procedure for Ene Reactions of Fluoral (2a) Catalyzed by (*R*)-BINOL-Derived Titanium Complex (1). To a suspension of MS 4Å (activated powder) (200 mg) in CH_2Cl_2 (2 mL) was added (*R*)-BINOL-derived titanium complex (**1**)[7b,d,e] (0.10 mmol) at room temperature. After stirring for 5 min, olefin (**3** or **6**) (1.0 mmol) and freshly dehydrated and distilled fluoral (**2a**) (*ca.* 2.0 eq) in CH_2Cl_2 (0.5 mL) was added to the mixture at 0 °C. After stirring for 30 min at that temperature, ether (2 mL) and sat. $NaHCO_3$ solution (2 mL) was added to the mixture. MS 4Å was filtered off through a pad of Celite and the filtrate was extracted three times with ether. The combined organic layer was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. Chromatographic separation by silica gel gave the product.

General Procedure for Ene Reactions of Chloral (2b) Catalyzed by (*R*)-BINOL-Derived Titanium Complex (1). To a suspension of MS 4Å (activated powder) (200 mg) in solvent (3 mL) was added (*R*)-BINOL-derived titanium complex (**1**) (0.10 mmol) at room temperature. After stirring for 5 min, olefin (**3**) (1.5 mmol) and chloral (**2b**) (1.0 mmol) was added to the mixture at 0 °C. After stirring for 2 h at that temperature, ether (2 mL) and sat. $NaHCO_3$ solution (2 mL) was added to the mixture. MS 4Å was filtered off through a pad of Celite and the filtrate was extracted three times with ether. The combined organic layer was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. Chromatographic separation by silica gel gave the product.

General Procedure for Ene Reactions of Difluoroacetaldehyde Ethyl Hemiacetal (10) Catalyzed by (*R*)-BINOL-Derived Titanium Complex (1). The reactions were carried out according to the general procedure described in ene reactions of chloral (**2b**) except for the use of difluoroacetaldehyde ethyl hemiacetal (1-ethoxy-2,2-difluoroethanol) (**10**) instead of chloral (**2b**). Difluoroacetaldehyde ethyl hemiacetal (**10**) was prepared as follows: To a solution of ethyl difluoroacetate (10.7 g, 82 mmol) in ether (15 mL) at -78 °C was added slowly a ether (25 mL) suspension of LAH (0.78g, 21 mmol) at -78 °C. After stirring for 15 min at that temperature, EtOH (3 mL) was added carefully into the resultant suspension. Then the mixture was warmed up to room temperature and then poured into ice water (10 mL) and H_2SO_4 (8 mL) mixture. The organic layer was separated and extracted with ether twice. Purification by distillation under reduced pressure gave difluoroacetaldehyde ethyl hemiacetal (**10**) in 76% yield: ^{1}H NMR ($CDCl_3$) δ 1.25 (m, 3H), 3.63 (dq, J = 7.0, 9.6 Hz, 1H), 3.92 (dq, J = 7.1, 9.6 Hz, 1H), 4.70 (ddd, J = 2.6, 7.8, 5.9 Hz, 1H), 5.60 (dt, J = 2.6, 55.5 Hz, 1H).

General Procedure for the Preparation of (*R*)- or (*S*)-MTPA Ester. The enantiomeric purities of the products were determined by ^{1}H NMR analysis after conversion to the (*R*)- or (*S*)-MTPA esters. To a solution of secondary alcohol (5 ~ 10 mg) in CH_2Cl_2 (0.5 mL) was added pyridine (2 ~ 3 drops), 4-dimethylaminopyridine (2 ~ 3 pieces) and MTPA chloride (1.5 eq). After stirring for 1 ~ 2 h at room temperature, the mixture was diluted with ether and washed with 0.5 *N* HCl and brine. The organic layer was dried over $MgSO_4$ and evaporated under reduced pressure. Chromatographic separation by silica gel gave the MTPA ester in quantitative yield.

3-(1-Cyclopentenyl)-1,1,1-trifluoro-2-propanol: ^{1}H NMR ($CDCl_3$) δ 1.93 (m, 2H), 2.20 ~ 2.39 (m, 4H), 2.32 (m, 1H), 2.47 (m, 1H), 4.08 (m, 1H), 5.61 (bs, 1H); ^{13}C NMR ($CDCl_3$) δ 22.7, 29.8, 29.8, 38.7, 67.9 (q, J = 31 Hz), 125.2 (q, J = 263 Hz), 127.0, 131.8; IR (neat) 3440, 2930, 1370, 1290, 1090 cm^{-1}; high resolution MS calcd for $C_8H_{11}F_3O$ (M^+) m/z 180.0762, found 180.0748.

3-Cyclopentylidene-1,1,1-trifluoro-2-propanol: ^{1}H NMR ($CDCl_3$) δ 1.62 ~ 1.79 (m, 4H), 2.35 (m, 4H), 4.56 (m, 1H), 5.47 (dq, J = 2.0, 8.7 Hz, 1H) ; ^{13}C NMR ($CDCl_3$) δ 26.5, 27.8, 28.3, 37.2, 66.8 (q, J = 30 Hz), 114.0, 125.2 (q, J = 263 Hz), 150.2; IR (neat) 3430, 3010, 1670, 1410, 1260, 1070 cm^{-1}.

(*R*)-MTPA Ester of 3-(1-Cyclopentenyl)-1,1,1-trifluoro-2-propanol: ^{1}H NMR ($CDCl_3$) δ 1.80 ~ 1.93 (m, 2H), 2.25 ~ 2.42 (m, 4H), 2.57 (m, 1H), 2.71 (m, 1H), 3.50 (bs, 3H), 5.33 (bs, 1H), 5.64 (m, 1H), 7.38 ~ 7.51 (m, 5H).

(*S*)-MTPA Ester of 3-(1-Cyclopentenyl)-1,1,1-trifluoro-2-propanol: ^{1}H NMR ($CDCl_3$) δ 1.80 ~ 1.93 (m, 2H), 2.25 ~ 2.42 (m, 4H), 2.57 (m, 1H), 2.71 (m, 1H), 3.56 (bs, 3H), 5.43 (bs, 1H), 5.70 (m, 1H), 7.38 ~ 7.51 (m, 5H).

(*R*)-MTPA Ester of 3-Cyclopentylidene-1,1,1-trifluoro-2-propanol: ^{1}H NMR ($CDCl_3$) δ 1.62 ~ 1.79 (m, 4H), 2.28 ~ 2.43 (m, 4H), 3.53 (s, 3H), 5.21 (dm, J = 9.6 Hz, 1H), 5.92 (dt, J = 6.5, 9.2 Hz, 1H), 7.38 ~ 7.51 (m, 5H).

(*S*)-MTPA Ester of 3-Cyclopentylidene-1,1,1-trifluoro-2-propanol: ^{1}H NMR ($CDCl_3$) δ 1.62 ~ 1.79 (m, 4H), 2.28 ~ 2.43 (m, 4H), 3.57 (s, 3H), 5.37 (dm, J = 9.6 Hz, 1H), 5.96 (dt, J = 6.5, 9.2 Hz, 1H), 7.38 ~ 7.51 (m, 5H).

3-(1-Cyclohexenyl)-1,1,1-trifluoro-2-propanol: ^{1}H NMR ($CDCl_3$) δ 1.59 (m, 2H), 1.66 (m, 2H), 2.04 (m, 4H), 2.20 (m, 1H), 2.39 (m, 1H), 4.03 (m, 1H), 5.63 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 22.1, 22.6, 27.9, 29.7, 38.6, 67.8 (q, J = 31 Hz), 126.9, 127.8 (q, J = 262 Hz), 131.7; IR (neat) 3440, 2920, 1430, 1260, 1090 cm^{-1}; high resolution MS calcd for $C_9H_{13}F_3O$ (M^+) m/z 194.0919, found 194.0929.

3-Cyclohexylidene-1,1,1-trifluoro-2-propanol: ^{1}H NMR ($CDCl_3$) δ 1.61 (m, 6H), 2.19 (m, 2H), 2.29 (m, 2H), 4.71 (m, 1H), 5.20 (m, J = 8.5Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 25.3, 26.4, 27.7, 28.2, 37.1, 66.8 (q, J = 31 Hz), 113.9, 127.8 (q, J = 262 Hz), 150.6; IR (neat) 2920, 2930, 1670, 1450, 1040 cm^{-1}.

(*R*)-MTPA Ester of 3-(1-Cyclohexenyl)-1,1,1-trifluoro-2-propanol: ^{1}H NMR ($CDCl_3$) δ 1.50 ~ 1.70 (m, 4H), 1.80 ~ 2.03 (m, 4H), 2.20 (m, 2H), 3.56 (s, 3H), 5.37 (bs, 1H), 5.61 (m, 1H), 7.35 ~ 7.68 (m, 5H).

(*S*)-MTPA Ester of 3-(1-Cyclohexenyl)-1,1,1-trifluoro-2-propanol: ^{1}H NMR ($CDCl_3$) δ 1.50 ~ 1.70 (m, 4H), 1.80 ~ 2.03 (m, 4H), 2.20 (m, 2H), 3.57 (s, 3H), 5.56 (bs, 1H), 5.65 (m, 1H), 7.35 ~ 7.68 (m, 5H).

(*R*)-MTPA Ester of 3-Cyclohexylidene-1,1,1-trifluoro-2-propanol: ^{1}H NMR ($CDCl_3$) δ 1.61 (m, 6H), 2.12 (m, 2H), 2.38 (m, 2H), 3.58 (s, 3H), 5.05 (d, J = 9.5 Hz, 1H), 6.12 (dt, J = 6.5, 9.6 Hz, 1H), 7.35 ~ 7.68 (m, 5H).

(*S*)-MTPA Ester of 3-Cyclohexylidene-1,1,1-trifluoro-2-propanol: ^{1}H NMR ($CDCl_3$) δ 1.61 (m, 6H), 2.12 (m, 2H), 2.38 (m, 2H), 3.59 (s, 3H), 5.23 (d, J = 9.5 Hz, 1H), 6.17 (dt, J = 6.5, 9.6 Hz, 1H), 7.35 ~ 7.68 (m, 5H).

1,1,1-Trichloro-3-(1-cyclopentenyl)-2-propanol: $[\alpha]_D^{24}$ = +5.37 (*c* 1.0, $CHCl_3$) (43% ee); ^{1}H NMR ($CDCl_3$) δ 1.93 (m, 2H), 2.36 (m, 4H), 2.49 (dd, J = 9.9, 15.0 Hz, 1H), 2.72 (d, J = 4.8 Hz, 1H), 2.86 (d, J = 15.0 Hz, 1H), 4.21 (dm, J = 9.6 Hz, 1H), 5.60 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 23.5, 32.6, 34.0, 35.1, 91.1, 103.7, 128.2, 139.3; IR (neat) 3400, 2930, 1670, 1440, 1390, 1290, 1100, 790 cm^{-1}; high resolution MS calcd for $C_8H_{11}{}^{35}Cl_3O$ (M^+) m/z 227.9877, found 227.9897.

1,1,1-Trichloro-3-cyclopentylidene-2-propanol: $[\alpha]_D^{24}$ = -31.46 (*c* 1.0, $CHCl_3$) (85% ee); ^{1}H NMR ($CDCl_3$) δ 1.69 (m, 4H), 2.38 (m, 4H), 2.69 (d, J = 5.7 Hz, 1H), 4.69 (dd, J = 5.4, 8.5 Hz, 1H), 5.47 (dm, J = 5.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 26.0, 26.3, 30.0, 34.3, 81.3, 103.7, 114.9, 154.6; IR (neat) 3200, 1680, 1430, 1300, 1260, 1100, 810 cm^{-1}; high resolution MS calcd for $C_8H_{11}{}^{35}Cl_3O$ (M^+) m/z 227.9877, found 227.9849.

(*R*)-MTPA Ester of 1,1,1-Trichloro-3-(1-cyclopentenyl)-2-propanol: ^{1}H NMR ($CDCl_3$) δ 1.80 ~ 1.93 (m, 2H), 2.10 ~ 2.50 (m, 4H), 2.66 ~ 3.10 (m, 2H), 3.57 (s, 3H), 5.36 (bs, 1H), 5.82 (dd, J = 2.0, 10.3 Hz, 1H), 7.34 ~ 7.61 (m, 5H).

(*S*)-MTPA Ester of 1,1,1-Trichloro-3-(1-cyclopentenyl)-2-propanol: ^{1}H NMR ($CDCl_3$) δ 1.80 ~ 1.93 (m, 2H), 2.10 ~ 2.50 (m, 4H), 2.66 ~ 3.10 (m, 2H), 3.60 (s, 3H), 5.51 (bs, 1H), 5.87 (dd, J = 2.0, 10.3 Hz, 1H), 7.34 ~ 7.61 (m, 5H).

(*R*)-MTPA Ester of 1,1,1-Trichloro-3-cyclopentylidene-2-propanol: ^{1}H NMR ($CDCl_3$) δ 1.73 (m, 4H), 2.28 ~ 2.70 (m, 4H), 3.57 (s, 3H), 5.33 (dm, J = 9.3 Hz, 1H), 6.06 (d, J = 9.3 Hz, 1H), 7.39 ~ 7.60 (m, 5H).

(*S*)-MTPA Ester of 1,1,1-Trichloro-3-cyclopentylidene-2-propanol: ^{1}H NMR ($CDCl_3$) δ 1.73 (m, 4H), 2.28 ~ 2.70 (m, 4H), 3.57 (s, 3H), 5.52 (dm, J = 9.3 Hz, 1H), 6.08 (d, J = 9.3 Hz, 1H), 7.39 ~ 7.60 (m, 5H).

1,1,1-Trichloro-3-(1-cyclohexenyl)-2-propanol: $[\alpha]_D^{24}$ = +2.23 (*c* 1.0, $CHCl_3$) (32% ee); ^{1}H NMR ($CDCl_3$) δ 1.06 (m, 2H), 1.66 (m, 2H), 2.04 (m, 4H), 2.25 (dd, J = 13.8, 10.0 Hz, 1H), 2.67 (m, 1H), 2.76 (d, J = 13.8 Hz, 1H), 4.16 (ddm, J = 2.3, 10.0 Hz, 1H), 5.65 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 22.2, 22.9, 25.4,

28.4, 40.8, 80.5, 103.7, 126.2, 133.1; IR (neat) 3440, 2920, 1430, 1260, 1090, 800 cm^{-1}; high resolution MS calcd for $C_9H_{13}{}^{35}Cl_3O$ (M^+) m/z 242.0034, found 242.0042.

1,1,1-Trichloro-3-cyclohexylidene-2-propanol: $[\alpha]_D{}^{24}$ = -10.64 (*c* 1.0, $CHCl_3$) (78% ee); ^1H NMR ($CDCl_3$) δ 1.60 (m, 6H), 2.19 (m, 2H), 2.28 (m, 2H), 2.69 (d, *J* = 5.8 Hz, 1H), 4.85 (dd, *J* = 5.8, 8.3 Hz, 1H), 5.29 (d, *J* = 8.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 26.5, 27.5, 28.3, 30.4, 37.4, 78.7, 103.7, 116.1, 150.0 IR (neat) 3400, 2170, 2930, 1670, 1450, 1270, 1050, 800, 740 cm^{-1}; high resolution MS calcd for $C_9H_{13}{}^{35}Cl_3O$ (M^+) m/z 242.0034, found 242.0005.

(*R*)-MTPA Ester of 1,1,1-Trichloro-3-(1-cyclohexenyl)-2-propanol: ^1H NMR ($CDCl_3$) δ 1.42 ~ 1.68 (m, 4H), 1.87 ~ 2.00 (m, 4H), 2.50 (m, 1H), 2.84(m, 1H), 3.56 (s, 3H), 5.39 (bs, 1H), 5.78 (dd, *J* = 1.7, 10.1 Hz, 1H), 7.38 ~ 7.62 (m, 5H).

(*S*)-MTPA Ester of 1,1,1-Trichloro-3-(1-cyclohexenyl)-2-propanol: ^1H NMR ($CDCl_3$) δ 1.42 ~ 1.68 (m, 4H), 1.87 ~ 2.00 (m, 4H), 2.50 (m, 1H), 2.84(m, 1H), 3.66 (s, 3H), 5.55 (bs, 1H), 5.81 (dd, *J* = 1.7, 10.1 Hz, 1H), 7.38 ~ 7.62 (m, 5H).

(*R*)-MTPA Ester of 1,1,1-Trichloro-3-cyclohexylidene-2-propanol: ^1H NMR ($CDCl_3$) δ 1.61 (m, 6H), 2.32 (m, 2H), 2.42 (m, 2H), 3.56 (s, 3H), 5.16 (d, *J* = 9.6 Hz, 1H), 6.27 (d, *J* = 9.4 Hz, 1H), 7.33 ~ 7.60 (m, 5H).

(*S*)-MTPA Ester of 1,1,1-Trichloro-3-cyclohexylidene-2-propanol: ^1H NMR ($CDCl_3$) δ 1.61 (m, 6H), 2.32 (m, 2H), 2.42 (m, 2H), 3.56 (s, 3H), 5.16 (d, *J* = 9.6 Hz, 1H), 6.27 (d, *J* = 9.4 Hz, 1H), 7.33 ~ 7.60 (m, 5H).

3-(1-Cyclohexenyl)-1,1,1-trifluoro-2-butanol (7a). *syn*-Isomer: $[\alpha]_D{}^{24}$ = +13.5 (*c* 1.0, $CHCl_3$) (98 : 2 *syn/anti*-mixture, 96% ee); ^1H NMR ($CDCl_3$) δ 1.12 (d, *J* = 7.0 Hz, 3H), 1.48 ~ 1.70 (m, 4H), 1.84 ~ 2.08 (m, 4H), 2.45 (m, 1H), 3.95 (m, 1H), 5.58 (bs, 1H); ^{13}C NMR ($CDCl_3$) δ 13.2, 22.5, 23.0, 25.4, 26.7, 41.3, 71.9 (q, *J* = 29 Hz), 123.9, 125.2 (q, *J* = 281 Hz), 137.8; high resolution MS calcd for $C_{10}H_{15}F_3O$ (M^+) m/z 208.1076, found 208.1077. ***anti*-Isomer:** ^1H NMR ($CDCl_3$) δ 1.12 (d, *J* = 7.0 Hz, 3H), 1.48 ~ 1.70 (m, 4H), 1.84 ~ 2.08 (m, 4H), 2.45 (m, 1H), 3.72 (m, 1H), 5.66 (bs, 1H).

3-Cyclohexylidene-1,1,1-trifluoro-2-butanol: ^1H NMR ($CDCl_3$) δ 1.48 ~ 1.70 (m, 8H), 1.60 (m, 3H), 1.80 ~ 1.93 (m, 2H), 5.01 (m, 1H).

(*R*)-MTPA Ester of *syn*-3-(1-Cyclohexenyl)-1,1,1-trifluoro-2-butanol (7a): ^1H NMR (C_6D_6) δ 0.81 (d, *J* = 6.9 Hz, 3H), 1.30 ~ 1.50 (m, 4H), 1.75 (m, 4H), 2.33 (m, 1H), 3.45 (s, 3H), 5.24 (bs, 1H) 5.61 (dq, *J* = 6.3, 6.9 Hz, 1H), 7.38 ~ 7.62 (m, 5H).

(*S*)-MTPA Ester of *syn*-3-(1-Cyclohexenyl)-1,1,1-trifluoro-2-butanol (7a): ^1H NMR (C_6D_6) δ 0.81 (d, *J* = 6.9 Hz, 3H), 1.30 ~ 1.50 (m, 4H), 1.75 (m, 4H), 2.33 (m, 1H), 3.45 (s, 3H), 5.38 (bs, 1H) 5.68 (dq, *J* = 6.3, 6.9 Hz, 1H), 7.38 ~ 7.62 (m, 5H).

(*R*)-MTPA Ester of 3-Cyclohexylidene-1,1,1-trifluoro-2-butanol: ^1H NMR (C_6D_6) δ 1.25 ~ 1.50 (m, 10H), 1.37 (m, 3H), 3.44 (s, 3H), 6.49 (q, *J* = 7.4 Hz, 1H), 7.38 ~ 7.62 (m, 5H).

(*S*)-MTPA Ester of 3-Cyclohexylidene-1,1,1-trifluoro-2-butanol: ^1H NMR (C_6D_6) δ 1.25 ~ 1.50 (m, 10H), 1.37 (m, 3H), 3.44 (s, 3H), 6.61 (q, *J* = 7.4 Hz, 1H), 7.38 ~ 7.62 (m, 5H).

3-(1-Cycloheptenyl)-1,1,1-trifluoro-2-butanol (7b). *syn*-Isomer: $[\alpha]_D{}^{24}$ = +8.7 ° (c 1.0, $CHCl_3$) (94:6 *syn/anti*-mixture, 95% ee); ^1H NMR ($CDCl_3$) δ 1.12 (d, *J* = 6.1 Hz, 3H), 1.65 ~ 1.85 (m, 8H), 2.05 (m, 2H), 2.31 (m, 1H), 2.63 (m, 1H), 3.90 (m, 1H), 5.72 (t, *J* = 6.3 Hz, 1H); high resolution MS calcd for $C_{11}H_{17}F_3O$ (M^+) m/z 222.1232, found 222.1235. ***anti*-Isomer:** ^1H NMR ($CDCl_3$) δ 1.12 (d, *J* = 6.1 Hz, 3H), 1.65 ~ 1.85 (m, 8H), 2.05 (m, 2H), 2.31 (m, 1H), 2.63 (m, 1H), 3.67 (m, 1H), 5.80 (t, *J* = 6.3 Hz, 1H).

3-Cycloheptylidene-1,1,1-trifluoro-2-butanol: ^1H NMR ($CDCl_3$) δ 1.32 ~ 1.63 (m, 8H), 1.58 (bs, 3H), 2.12 (m, 4H), 2.31 (m, 1H), 4.99 (m, 1H).

(*R*)-MTPA Ester of *syn*-3-(1-Cycloheptenyl)-1,1,1-trifluoro-2-butanol (7b): ^{1}H NMR (C_6D_6) δ 0.89 (d, *J* = 6.8 Hz, 3H), 1.40 ~ 1.60 (m, 4H), 1.73 (m, 4H), 2.09 (m, 2H), 2.62 (m, 1H), 3.58 (s, 3H), 5.46 (t, *J* = 6.7 Hz, 1H), 5.55 (t, *J* = 6.3, Hz, 1H), 7.38 ~ 7.70 (m, 5H).

(*S*)-MTPA Ester of *syn*-3-(1-Cycloheptenyl)-1,1,1-trifluoro-2-butanol (7b): ^{1}H NMR (C_6D_6) δ 0.89 (d, *J* = 6.8 Hz, 3H), 1.40 ~ 1.60 (m, 4H), 1.73 (m, 4H), 2.09 (m, 2H), 2.62 (m, 1H), 3.58 (s, 3H), 5.41 (t, *J* = 6.7 Hz, 1H), 5.66 (t, *J* = 6.3, Hz, 1H), 7.38 ~ 7.70 (m, 5H).

1,1,1-Trifluoro-3,4-dimethyl-4-penten-2-ol (7c). *syn*-Isomer: $[\alpha]_D^{24}$ = +2.9 (*c* 1.0, CHCl3) (91 : 9 *syn/anti*-mixture, 78% ee); ^{1}H NMR ($CDCl_3$) δ 1.18 (d, *J* = 7.0 Hz, 3H), 1.72 (bs, 3H), 2.18 (m, 1H), 2.59 (m, 1H), 3.98 (m, 1H), 4.88 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 13.3, 14.2, 40.9, 71.7 (q, *J* = 29 Hz), 112.9, 127.7 (q, *J* = 282 Hz), 135.4. ***anti*-Isomer:** ^{1}H NMR ($CDCl_3$) δ 1.18 (d, *J* = 7.0 Hz, 3H), 1.72 (bs, 3H), 2.18 (m, 1H), 2.59 (m, 1H), 3.78 (m, 1H), 4.88 (m, 2H).

1,1,1-Trifluoro-3,4-dimethyl-3-penten-2-ol: ^{1}H NMR ($CDCl_3$) δ 1.76 (bs, 6H), 1.78 (s, 3H), 2.23 (m, 1H), 4.96 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 20.6, 20.6, 22.4, 69.5 (q, *J* = 31 Hz), 102.2, 127.7 (q, *J* = 282 Hz), 145.8.

(*R*)-MTPA Ester of *syn*-1,1,1-Trifluoro-3,4-dimethyl-4-penten-2-ol (7c): ^{1}H NMR ($CDCl_3$) δ 0.95 (d, *J* = 6.9 Hz, 3H), 1.74 (bs, 3H), 2.65 (m, 1H), 3.58 (s, 3H) 4.75 (d, *J* = 33.8, 2H), 5.55 (m, 1H), 7.39 ~ 7.56 (m, 5H).

(*S*)-MTPA Ester of *syn*-1,1,1-Trifluoro-3,4-dimethyl-4-penten-2-ol (7c): ^{1}H NMR ($CDCl_3$) δ 1.13 (d, *J* = 6.9 Hz, 3H), 1.74 (bs, 3H), 2.71 (m, 1H), 3.58 (s, 3H) 4.87 (d, *J* = 33.8, 2H), 5.44 (m, 1H), 7.39 ~ 7.56 (m, 5H).

(*R*)-MTPA Ester of 1,1,1-Trifluoro-3,4-dimethyl-3-penten-2-ol: ^{1}H NMR ($CDCl_3$) δ 1.55 (m, 3H), 1.80 (m, 3H), 1.85 (m, 3H), 3.59 (s, 3H), 4.64 (bs, 1H), 7.38 ~ 7.56 (m, 5H).

(*S*)-MTPA Ester of 1,1,1-Trifluoro-3,4-dimethyl-3-penten-2-ol: ^{1}H NMR ($CDCl_3$) δ 1.55 (m, 3H), 1.80 (m, 3H), 1.85 (m, 3H), 3.59 (s, 3H), 4.58 (bs, 1H), 7.38 ~ 7.56 (m, 5H).

***syn*-5,5,5-Trifluoro-4-hydroxy-3-methyl-2-pentanone (8c).** A stream of ozone was bubbled into a solution of *syn*-1,1,1-trifluoro-3,4-dimethyl-4-penten-2-ol (**7c**) in MeOH at -78 °C untill the colour of the solution was turned pale blue. After removal of excess ozone by dry nitrogen gas, the resultant mixture was treated with dimethyl sulfide (1 mL) and warmed up to room temperature. After evaporated under reduced pressure, the residue was diluted with water and extracted with ether. The organic layer was washed with brine and dried over $MgSO_4$. Removal of the solvent under reduced pressure followed by chromatographic separation by silica gel gave *syn*-5,5,5-trifluoro-4-hydroxy-3-methyl-2-pentanone (**8c**): ^{1}H NMR ($CDCl_3$) δ 1.31 (d, *J* = 7.3 Hz, 3H), 2.25 (s, 3H), 2.92 (dq, *J* = 4.2, 7.4 Hz, 1H), 4.45 (dq, *J* = 4.2, 7.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 10.44, 28.5, 46.2, 69.3 (q, *J* = 31 Hz), 125.0 (q, *J* = 281 Hz), 210.9.

1-[3,3,3-Trifluoro-1-methyl-1-(*E*)-propenyl]cyclohexene [(*E*)-9a]. To a solution of *syn*-(1-cyclohexenyl)-1,1,1-trifluoro-2-butanol (**7a**) (208 mg, 1 mmol) in pyridine (0.5 mL) $POCl_3$ (0.09mL, 1 mmol) was added at 0 °C, and the mixture was stirred at 110 °C for 48 h. After cooling, the mixture was treated with ice water and extracted with ether, and dried over $MgSO_4$. Removal of the solvent under reduced pressure followed by chromatographic separation by silica gel gave 1-[3,3,3-trifluoro-1-methyl-1-(*E*)-propenyl]cyclohexene [(*E*)-**9a**]: ^{1}H NMR ($CDCl_3$) δ 1.59 (m, 2H), 1.68 (m, 2H), 2.00 (s, 3H), 2.12 ~ 2.19 (m, 4H), 5.57 (q, *J* = 8.80 Hz, 1H), 6.17 (bs, 1H); ^{13}C NMR ($CDCl_3$) δ 14.6, 21.8, 22.6, 25.6, 26.0, 112.4 (q, *J* = 33 Hz), 124.8 (q, *J* = 227 Hz), 129.7, 136.2, 148.8.

1-[3,3,3-Trifluoro-1-methyl-1-(*Z*)-propenyl]cyclohexene [(*Z*)-9a]. To a solution of 1-[3,3,3-trifluoro-1-methyl-1-(*E*)-propenyl]cyclohexene [(*E*)-**9a**] (95 mg, 0.5 mmol) in ether (5 mL) was added benzophenone (5 mg). The mixture was irradiated with high-pressure mercury lamp for 1 h. Removal of the solvent under reduced pressure followed by chromatographic separation by silica gel gave 1-[3,3,3-trifluoro-1-

methyl-1-(*Z*)-propenyl]cyclohexene [(*Z*)-**9a**]: ^{1}H NMR ($CDCl_3$) δ 1.56 ~ 1.75 (m, 4H), 1.89 (bs, 3H), 2.00 ~ 2.15 (m, 4H), 5.34 (m, 1H), 5.53 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 21.8, 22.5, 23.9, 24.9, 27.1, 113.8 (q, J = 33 Hz), 123.3 (q, J = 269 Hz), 124.6, 136.5, 153.6.

3-(1-Cyclopentenyl)-1,1-difluoro-2-propanol (11): $[\alpha]_D^{26}$ = +26.8 (*c* 1.0, $CHCl_3$) (>95% ee); ^{1}H NMR ($CDCl_3$) δ 1.90 (m, 2H), 2.04 (m, 2H), 2.29 (m, 2H), 2.38 (m, 2H), 3.92 (m, 1H), 5.57 (dt, J = 3.9, 56.0 Hz, 1H), 5.57 (bs, 1H); ^{13}C NMR ($CDCl_3$) δ 23.5, 32.1, 32.6, 35.1, 69.2 (t, J = 23 Hz), 116.1 (t, J = 242 Hz), 128.5, 138.8.

3-Cyclopentylidene-1,1-difluoro-2-propanol (12): ^{1}H NMR ($CDCl_3$) δ 1.92 (m, 2H), 2.20 ~ 2.40 (m, 6H), 4.42 (m, 1H), 5.33 (m, 1H), 5.65 (dt, J = 3.9, 56.0 Hz, 1H).

(*R*)-MTPA Ester of 3-(1-Cyclopentenyl)-1,1-difluoro-2-propanol (11): ^{1}H NMR ($CDCl_3$) δ 1.81 (m, 2H), 2.00 ~ 2.30 (m, 4H), 2.48 (m, 2H), 3.56 (s, 3H), 5.35 (m, 1H), 5.43 (m, 1H), 5.82 (dt, J = 3.9, 56.0 Hz, 1H), 7.38 ~ 7.53 (m, 5H).

(*S*)-MTPA Ester of 3-(1-Cyclopentenyl)-1,1-difluoro-2-propanol (11): ^{1}H NMR ($CDCl_3$) δ 1.81 (m, 2H), 2.00 ~ 2.30 (m, 4H), 2.48 (m, 2H), 3.56 (s, 3H), 5.48 (m, 1H), 5.52 (m, 1H), 5.73 (dt, J = 3.9, 56.0 Hz, 1H), 7.38 ~ 7.53 (m, 5H).

Typical Procedure for Aldol Reaction with Fluoral: *S-tert*-Butyl 4,4,4-Trifluoro-3-hydroxybutanethioate (14a). To a solution of the chiral titanium complex, (*R*)-BINOL-$TiCl_2$ (**1**) (0.20 mmol) in toluene (3 mL) was added KSA (**13a**) (1.0 mmol) and a toluene (0.5 mL) solution of fluoral (**2a**) (*ca.* 2.0 eq) separately but simultaneously over several minutes at 0 °C. After stirring for 10 min at that temperature, ether (2 mL) and sat. $NaHCO_3$ solution (2 mL) was added to the reaction mixture. The solution was filtered through a pad of Celite and the filtrate was extracted three times with ether (totally 15 mL). The combined organic layer was washed with brine. The extract was then dried over $MgSO_4$ and evaporated under reduced pressure to give the crude product as a silyl ether form. The crude product was treated with 10% HCl-MeOH. Separation of the resultant mixture by silica gel chromatography (*n*-hexane/AcOEt = 20 : 1) gave *S-tert*-butyl 4,4,4-trifluoro-3-hydroxybutanethioate (**14a**) in 56% yield: $[\alpha]_D^{28}$ = +26.2 (*c* 1.65, $CHCl_3$) (87% ee); Chiral HPLC analysis (stationary phase: Daicel CHIRALCEL OD, mobile phase: *n*-hexane/*i*-PrOH = 50 : 1, 0.5 mL/min) t_R[(*R*)-isomer] = 22.1 min, t_R[(*S*)-isomer] = 17.7 min; ^{1}H NMR ($CDCl_3$) δ 1.48 (s, 9H), 2.82 (dd, J = 7.6, 16.2 Hz, 1H), 2.84 (dd, J = 4.1, 16.2 Hz, 1H), 3.15 ~ 3.45 (m, 1H), 4.38 ~ 4.53 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 29.7, 43.4, 49.3, 67.7 (q, J = 32 Hz), 124.0 (q, J = 280 Hz), 198.2; IR (neat) 3450, 2970, 1680, 1460, 1370, 1280, 1140, 670 cm^{-1}; high resolution MS calcd for $C_8H_{13}F_3O_2S$ (M^+) m/z 230.0589, found 230.0586.

***S*-Phenyl 4,4,4-Trifluoro-3-hydroxybutanethioate (14b):** $[\alpha]_D^{28}$ = +37.7 (*c* 1.10, $CHCl_3$) (96% ee); ^{1}H NMR ($CDCl_3$) δ 3.05 (d, J = 6.5 Hz, 2H), 3.20 (d, J = 5.5 Hz, 1H), 4.44 ~ 4.60 (m, 1H), 7.40 ~ 7.50 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 42.9, 67.4 (q, J = 33 Hz), 124.4 (q, J = 280 Hz), 129.6, 130.2, 134.7, 195.9; high resolution MS calcd for $C_{10}H_9F_3O_2S$ (M^+) m/z 250.0276, found 250.0254.

(*R*)-MTPA Ester of *S*-Phenyl 4,4,4-Trifluoro-3-hydroxybutanethioate (14b): ^{1}H NMR ($CDCl_3$) δ 2.43 (dd, J = 2.6, 17.0 Hz, 1H), 2.72 (dd, J = 10.4, 17.0 Hz, 1H), 3.49 (s, 3H), 6.07 ~ 6.21 (m, 1H), 7.03 ~ 7.72 (m, 10H).

(*S*)-MTPA Ester of *S*-Phenyl 4,4,4-Trifluoro-3-hydroxybutanethioate (14b): ^{1}H NMR ($CDCl_3$) δ 2.48 (dd, J = 2.5, 17.0 Hz, 1H), 2.80 (dd, J = 10.5, 17.0 Hz, 1H), 3.43 (s, 3H), 6.05 ~ 6.20 (m, 1H), 7.00 ~ 7.78 (m, 10H).

Ethyl 4,4,4-Trifluoro-3-hydroxy-2-methylbutanethioate (16). *syn*-Isomer: Chiral HPLC analysis (stationary phase: Daicel CHIRALCEL OD, mobile phase: *n*-hexane/*i*-PrOH = 200 : 1, 0.8 mL/min) t_R[(2*R*,3*R*)-isomer] = 43.4 min, t_R[(2*S*,3*S*)-isomer] = 40.6 min; ^{1}H NMR ($CDCl_3$) δ 1.27 (t, J = 7.4 Hz, 3H), 1.37 (d, J = 7.2 Hz, 3H), 2.91 (q, J = 7.4 Hz, 2H), 3.01 (dq, J = 4.0, 7.2 Hz, 1H), 4.37 ~ 4.48 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 12.1, 14.6, 23.7, 47.6, 70.3 (q, J = 31 Hz), 124.4 (q, J = 281 Hz), 202.0; IR (neat) 3420, 2940,

1670, 1460, 1380, 1270, 1150, 690 cm^{-1}; high resolution MS calcd for $C_7H_{11}F_3O_2S$ (M^+) m/z 216.0432, found 216.0427. ***anti*-Isomer:** Chiral HPLC analysis (stationary phase: Daicel CHIRALCEL OD, mobile phase: *n*-hexane/*i*-PrOH = 200 : 1, 0.8 mL/min) t_R[(2*S*,3*R*)-isomer] = 41.9 min, t_R[(2*R*,3*S*)-isomer] = 21.6 min; ^1H NMR ($CDCl_3$) δ 1.27 (t, *J* = 7.4 Hz, 3H), 1.40 (d, *J* = 7.2 Hz, 3H), 2.91 (dq, *J* = 3.0, 7.4 Hz, 1H), 3.02 (dq, *J* = 4.0, 7.2 Hz, 1H), 3.94 ~ 4.06 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 14.5, 16.3, 23.7, 46.1, 73.5 (q, *J* = 31 Hz), 125.0, (q, *J* = 249 Hz), 203.5; IR (neat) 3470, 2940, 1670, 1460, 1380, 1280, 1140, 660 cm^{-1}; high resolution MS calcd for $C_7H_{11}F_3O_2S$ (M^+) m/z 216.0432, found 216.0441.

***S*-*tert*-Butyl 4,4-Difluoro-3-hydroxy-butanethioate (17):** $[\alpha]_D^{28}$ = +17.6 (*c* 1.15, $CHCl_3$) (95% ee); Chiral HPLC analysis (stationary phase: Daicel CHIRALCEL OD, mobile phase: *n*-hexane/*i*-PrOH = 50 : 1, 0.5 mL/min) t_R[(*R*)-isomer] = 25.5 min, t_R[(*S*)-isomer] = 22.3 min; ^1H NMR ($CDCl_3$) δ 1.48 (s, 9H), 2.75 (dd, *J* = 8.1, 16.1 Hz, 1H), 2.83 (dd, *J* = 4.5, 16.1 Hz, 1H), 3.02 (d, *J* = 4.9 Hz, 1H), 4.15 ~ 4.32 (m, 1H), 5.75 (dt, *J* = 3.6, 55.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 29.7, 43.3, 49.1, 68.4 (t, *J* = 25 Hz), 115.3 (t, *J* = 243 Hz), 199.2; IR (neat) 3460, 2970, 1670, 1460, 1370, 1260, 1070, 670, 660 cm^{-1}; high resolution MS calcd for $C_8H_{14}F_2O_2S$ (M^+) m/z 212.0683, found 212.0687.

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