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Diastereoselective and Enantioselective Catalysis of the Carbonyl-Ene Reaction with Fluoral

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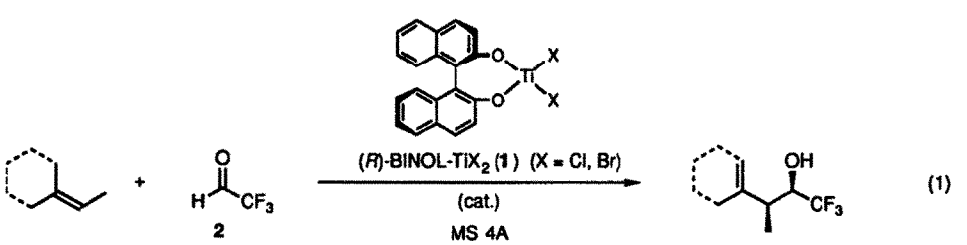
Abstract: The chiral titanium complex-catalyzed carbonyl-ene reaction with fluoral is shown to serve as an efficient route for the *syn*-diastereoselective and enantioselective synthesis of CF_3-substituted compounds of biological and synthetic importance.

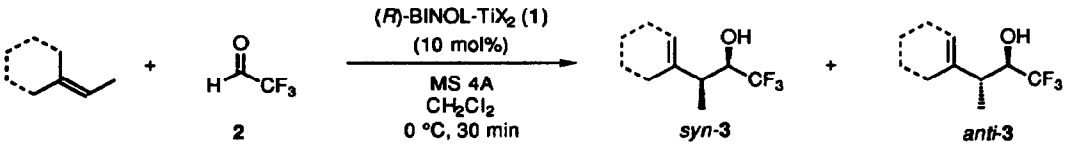
Organofluorine compounds are commonly employed in medicinal and biological chemistry. Recently, chiral organofluorine compounds are also finding abiological applications in material science such as electronics and optics. Thus, there is much research activity to develop methods for the asymmetric synthesis of organofluorine compounds and to provide a deeper insight into the effect of fluorine on physiological and physical properties.[1] This class of compounds with unexpected reactivity are often difficult to synthesize and hence coin the term flustrates: fluorine-containing substrates.[2] Highly enantiopure flustrates have been thus far obtained mainly by enzymatic or biological methods.[3] However, homogeneous asymmetric catalysis by chiral metal complexes[4] now rivals the biological approach even for the asymmetic synthesis of flustrates. An attractive feature of these man-made, non-enzymatic catalysts is that both enantiomorphs are usually available. Recently, asymmetric catalytic carbonyl-ene reaction has been emerging as an efficient method for asymmetric carbon skeleton construction (carbon-carbon bond formation).[5,6] We now wish to report herein the diastereo- and enantioselective catalysis of the carbonyl-ene reaction with fluoral (**2**) which provides an efficient route for the asymmetric synthesis of CF_3-containing compounds with high level of stereocontrol in both the absolute and relative sense, by chiral binaphthol-derived titanium (BINOL-Ti) complex (**1**)[5,6a] (eq. 1).[7]



(1)

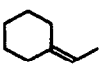
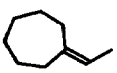
The reaction was carried out simply by adding freshly dehydrated and distilled fluoral (**2**) and then the olefin at 0 °C to the dichloromethane solution of chiral titanium dihalide (**1**) (10 mol%) prepared from (*R*)-binaphthol and diisopropoxytitanium dihalide as described for glyoxylate-ene reaction.[6a] The reaction was

completed within 30 min (monitored by TLC). Usual work-up followed by column chromatography provided good isolated yields of the homoallylic alcohol products (**3**) with high levels of *syn*-diastereo- and enantioselectivities.[8] The diastereomeric ratios of the fluoral-ene products (**3**) are determined by the ^{1}H NMR analysis. The enantiomeric purities of products were determined by ^{1}H NMR analysis after transformation to the (*S*)- and (*R*)-MTPA ester derivatives.[9] The absolute configuration of the products (**3**) was determined by the Mosher method.[9] Thus, the sense of asymmetric induction is exactly the same as observed for the glyoxylate-ene reaction; (*R*)-**1** provides (*R*)-*syn*-alcohols (**3**). Table I summarizes the representative results of the *syn*-diastereo- and enantioselective catalysis of fluoral-ene reaction.



2 *syn*-**3** *anti*-**3**

Table I. Asymmetric catalytic fluoral-ene reaction.[a]

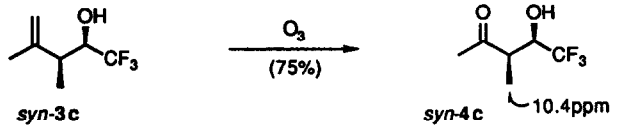
Entry	Olefin	1 (X)	%yield	*syn*-3	:	*anti*-3
1		Cl	94	98 (96% ee)	:	2
2	**a**	Br	85	96 (92% ee)	:	4
3		--[b]	46	96	:	4
4		Cl	76	94 (95% ee)	:	6
5	**b**	Br	75	98 (93% ee)	:	2
6		Cl	66	91 (78% ee)	:	9
7	**c**	Br	74	96 (74% ee)	:	4

[a] All reactions were carried out with 0.1 mmol (10 mol%) of **1**, 1.0 mmol of olefin, and *ca.* 2.0 mmol of **2** in the presence of MS 4A (0.2 g), unless otherwise marked. [b] An equimolar amount of Me_2AlCl was used.

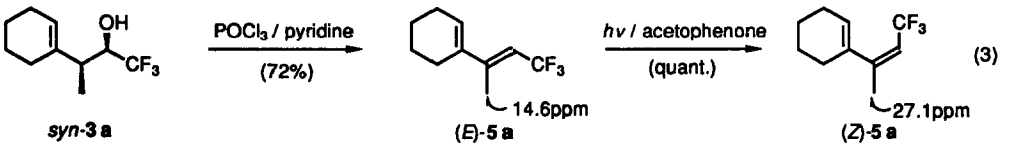
Inspection of Table I indicates several characteristic features of the asymmetric catalytic fluoral-ene reactions. All the fluoral-ene reactions provide the *syn*-homoallylic alcohols (**3**) with remarkably high level of diastereoselectivity. Significantly, high enantiomeric excesses (~96% ee) were observed for the *syn*-homoallylic alcohol products (**3**), except for the reaction with 2-methyl-2-butene (74~78% ee).[10] Thus, the catalytic ene reaction involving fluoral enophile provides an efficient route to the *syn*-diastereo- and enantioselective synthesis of CF_3-containing compounds, by the catalysis of BINOL-Ti catalyst (**1**).

The stereochemical assignment of the diastereomers of the fluoral-ene products deserves special comment. The *syn*-diastereomer of the fluoral-ene product with 2-methyl-2-butene was assigned by ^{13}C NMR analysis through ozonolysis to the aldol-type α-methyl-β-hydroxy ketone (**4c**) (eq. 2). The α-methyl carbon absorbs in the range of *syn*-diatereomers (10.4 ppm).[11] The *syn*-configuration was further determined after

stereospecific transformation to the dienes (**5**) by *anti*-elimination ($POCl_3$, pyridine) (eq. 3).[7a] The most definitive distinguishing feature is the ^{13}C NMR signals of the olefinic CH_3 carbon of the diene (**5a**) obtained by the *anti*-elimination of the fluoral-ene product (**3a**). Thus, the resultant diene, which shows the CH_3 carbon signal at higher field (14.6 ppm) than that (27.1 ppm) of the other photo-isomerized product, can be assigned to (*E*)-**5a**. Thus, the major diastereomer of the fluoral-ene product is assigned to be *syn*-isomer.



syn-**3c** *syn*-**4c** (2)



syn-**3a** (*E*)-**5a** (*Z*)-**5a** (3)

The *syn*-diastereoselectivity is analogous to that of the alkylaluminum triflate-promoted glyoxylate-ene reaction with *trans*- and *cis*-2-butene (also see: Table I, entry 3).[12] This suggests that the present fluoral-ene reaction also proceeds through the monodentate complex (**A**) rather than the bidentate complex (**B**).[13]

A **B**

In summary, we have reported that the *syn*-diastereo- and enantioselective catalysis of fluoral-ene reaction by the chiral titanium complex (**1**), which provides an asymmetric route for the CF_3-substituted compounds of biological and synthetic importance. Further work along this line is now under active investigation.

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