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Asymmetric Catalysis of Ene-type Reaction with Fluoral by Chiral Titanium Complex: A Semi-empirical and Ab-initio Analysis of Ene Reactivity

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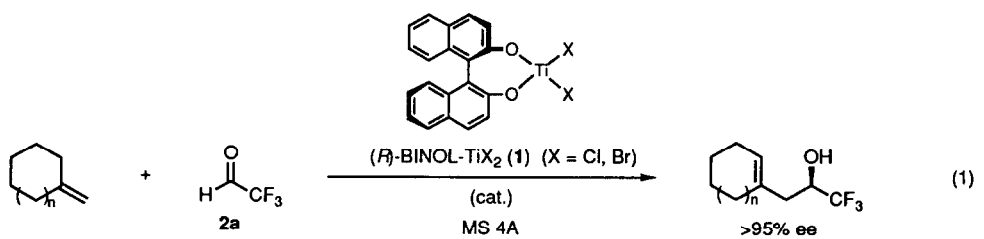
Abstract: The chiral titanium complex-catalyzed ene-type reaction with fluoral is shown to serve as an efficient route for the asymmetric synthesis of CF_3-substituted compounds of biological and synthetic importance in extremely high enantiomeric excesses (>95% ee). The ene reactivity of trihaloacetaldehyde including fluoral is estimated in terms of the balance of LUMO energy level *vs.* electron density on the carbonyl carbon.

Recently, asymmetric catalytic carbonyl-ene reaction has been emerging as an efficient method for asymmetric carbon-carbon bond formation.[1] However, only limited types of aldehyde enophile have been explored thus far.[2] We now wish to report the asymmetric catalysis of carbonyl-ene reaction with fluoral (**2a**) which provides an efficient route for the asymmetric synthesis of CF_3-containing compounds of biological and synthetic importance[3] in unprecedentedly high level of enantiomeric excess (>95% ee) by using chiral binaphthol-derived titanium (BINOL-Ti) complex (**1**)[1,2a] (eq. 1).[4] Detailed below are the asymmetric catalysis of ene-type reaction with fluoral and the analysis of the ene reactivity based on the semi-empirical and ab-initio molecular orbital calculations.



(1)

The reaction was carried out just by simply adding freshly dehydrated and distilled fluoral (**2a**) and then olefin at 0 °C to the solution of chiral titanium dihalide (**1**) (10 mol%) prepared from (*R*)- or (*S*)-binaphthol and diisopropoxytitanium dihalide as described for glyoxylate-ene reaction.[2a] The reaction was completed within 30 min (monitored by TLC). Usual work-up followed by column chromatography provided the good isolated yields of the homoallylic (**3**) and allylic (**4**) alcohol products. The enantiomeric purities of both products were determined to be almost perfect (>95% ee) by ^1H NMR analysis after transformation to the (*S*)-(-)- and (*R*)-(+)-MTPA ester derivatives.[5] The

To the memory of the late Professor Nobuo Ishikawa.

absolute configuration of the products (**3** and **4**) was determined by the Mosher method.[5] The sense of asymmetric induction is, therefore, exactly the same as observed for the glyoxylate-ene reaction; (*R*)-**1** provides (*R*)-**3** and -**4**. Table I summarizes the representative results of the asymmetric catalytic ene-type reaction with trihaloacetaldehydes including chloral (**2b**) as a reference.

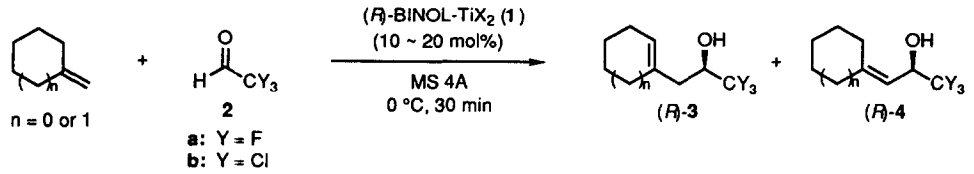


Table I. Asymmetric catalytic ene-type reaction with trihaloacetaldehydes.[a]

Entry	2	1 (X)	olefins (n)	solvent	%yield	3	(% ee)	:	4	(%ee)
1	**2a**	Cl	0	CH_2Cl_2	78	62	(>95% ee)	:	38	(>95% ee)
2	**2a**	Cl	1	CH_2Cl_2	93	76	(>95% ee)	:	24	(>95% ee)
3	**2a**	Br	1	CH_2Cl_2	95	79	(>95% ee)	:	21	(>95% ee)
4	**2a**	Cl	0	toluene	82	77	(>95% ee)	:	23	(>95% ee)
5	**2a**	Cl	1	toluene	82	79	(>95% ee)	:	21	(>95% ee)
6	**2b**	Cl	0	CH_2Cl_2	57	55	(26% ee)	:	45	(75% ee)
7[b]	**2b**	Br	0	CH_2Cl_2	84	59	(37% ee)	:	41	(85% ee)
8	**2b**	Cl	1	CH_2Cl_2	49	52	(34% ee)	:	48	(66% ee)
9[b]	**2b**	Br	1	CH_2Cl_2	40	48	(45% ee)	:	52	(80% ee)
10[b]	**2b**	Cl	1	toluene	35	63	(11% ee)	:	37	(66% ee)

[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] 0.2 mmol (20 mol%) of **1** was employed.

Inspection of Table I indicates several characteristic features of the asymmetric catalytic ene-type reaction with trihaloacetaldehydes. (1) Of particular interest is that the ratio of the homoallylic (**3**) and allylic (**4**) alcohol products depends heavily on the nature of the halogen substituents. (2) The enantiomeric excesses of the ene-type reactions also rely on the halogen substituents. (3) Amongst, fluoral provides remarkably high levels of enantiomeric excesses (>95% ee) for both the homoallylic (**3**) and allylic (**4**) alcohol products. (4) Thus, the catalytic ene type-reaction involving fluoral enophile 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**).

Of mechanistic interest is the significant influence of the halogen substituents not only on the product ratio but also on the enantiomeric excesses of homoallylic (**3**) and allylic (**4**) alcohol products. Thus, the ene reactivity of trihaloacetaldehydes was estimated on the basis of the atomic charge and LUMO energy level (MNDO, PM3, and 6-31G**).[6,7,8] The refined results were obtained using the split-valence basis set with polarization functions (6-31G**). The results from semi-empirical (MNDO and PM3) and ab-initio (6-31G**) calculations were very comparable (Table II).

Table II. 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 calculation was run on the aldehyde (**2**) / H^+ complexes as a model of **2** / Lewis acid complexes.

Inspection of Table II leads to MO analysis of the ene *vs.* cationic reactivity of trihaloacetaldehydes. The frontier orbital interaction between the HOMO of the ene component 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 species to give mainly the homoallylic alcohols (**3**) and chloral (**2b**) complex with the higher LUMO energy level is the less reactive one. In contrast, chloral complex bears the greater positive charge at the carbonyl carbon (C_1) and hence is the more reactive compound in terms of the cationic (Friedel-Crafts-type) reaction leading eventually to the allylic alcohols (**4**). Interestingly, the data reveals that the positive charge of the acetaldehyde (**2c**) carbonyl carbon is greater than the fluoral (**2a**).[9] 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).

In summary, we have reported that the chiral titanium complex-catalyzed ene-type reaction with fluoral provides an asymmetric route for the CF_3-substituted compounds of biological and synthetic importance, and that the ene reactivity of trihaloacetaldehyde including fluoral was estimated in terms of the balance of the LUMO level vs. atomic charges of reaction sites of the enophile components. Further works along this line is now under active investigations.

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