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Diastereoselective and Enantioselective Glyoxylate-Ene Reaction Catalyzed by New Class of Binaphthol-Derived Titanium Complex

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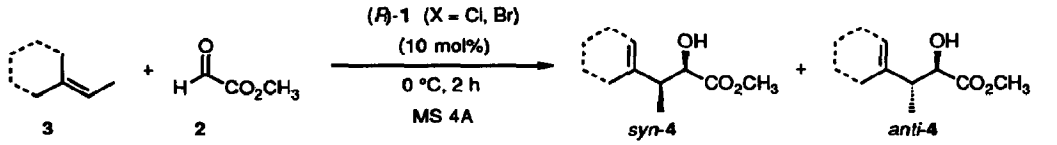
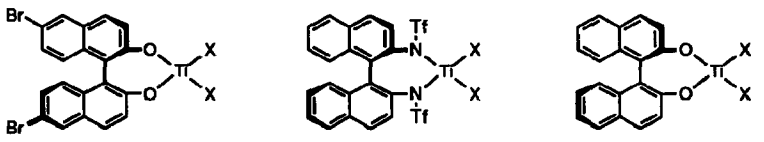
Abstract: Diastereo- and enantioselective carbonyl-ene reaction of glyoxylate (**2**) with trisubstituted olefins (**3**) catalyzed by chiral titanium complexes (**1a**), derived from 6,6'-dibromo-1,1'-bi-2-naphthol and diisopropoxytitanium dihalides, is found to provide *syn*-diastereomers exclusively along with a high level of enantioselectivity.

Recently, much attention has been paid to the development of asymmetric catalysis, particularly of carbon-carbon bond forming reaction.[1] Among others, catalytic stereocontrol not only in absolute sense but also in relative sense is one of the most challenging and formidable endeavor in organic synthesis. We now wish to report herein the diastereoselective and enantioselective carbonyl-ene reaction[2] of glyoxylate (**2**) with trisubstituted olefins (**3**) catalyzed by modified binaphthyl-derived chiral titanium dihalide complexes (**1a** and **b**) (eq 1), which provides an efficient access to the asymmetric synthesis of α-hydroxy-β-methyl esters.



3 **2** *syn*-**4** *anti*-**4** (1)



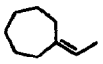
(*R*)-**1a** (*R*)-**1b** (*R*)-**1c**

We have previously reported that the binaphthol-derived chiral titanium complexes (**1c**) are quite effective for the enantioselective glyoxylate-ene reaction with 1,1-disubstituted olefins.[3] Unfortunately however, the reaction with trisubstituted olefins (**3**) provides only a low to moderate

level of enantioselectivity, despite a high level of *syn*-diastereoselectivity (*vide infra*). In order to enhance the insufficient level of enantioselectivity, we have examined new types of binaphthyl-derived chiral titanium complexes (**1a** and **1b**).

The reaction was carried out in a similar manner as described for the enantioselective glyoxylate-ene reaction.[3] The chiral titanium dihalide complexes (**1**) (10 mol%) were prepared from (*R*)-binaphthyl derivatives[4] and diisopropoxytitanium dihalides. A freshly distilled glyoxylate (**2**) and olefin (**3**) were added into the solution of **1** suspended with MS 4A at 0 °C. After 2 h, usual work-up followed by silica gel column chromatography gave diastereomeric ene products (**4**) in moderate to good isolated yields. The diastereoselectivity was determined by ^{1}H NMR analysis.[5,6] The enantiomeric purity was determined by ^{1}H NMR analysis after transformation to the corresponding (*S*)- and (*R*)-MTPA ester derivatives. The absolute stereochemistry was determined by the Mosher method.[7] Thus, the sense of asymmetric induction is exactly the same as that of enantioselective glyoxylate-ene reactions catalyzed by **1c**:[3] (*R*)-catalysts provide (2*R*)-α-hydroxy esters (**4**). Table 1 summarizes the representative results of the glyoxylate-ene reactions with trisubstituted olefins (**3**).

Table 1. Diastereo- and Enantioselective Glyoxylate-Ene Reaction Catalyzed by Titanium Complex **1**.[a]

Entry	**1** (X)	**3**	solvent	%yield	*syn*	:	*anti*
1	**1a** (Cl)		CH_2Cl_2	44	**93** (**81%** ee)	:	7
2	**1c** (Cl)		CH_2Cl_2	42	84 (68% ee)	:	16
3[b]	**1a** (Cl)		toluene	60	**93** (**88%** ee)	:	7
4	**1b** (Cl)		toluene	52	78 (3% ee)	:	22
5[b]	**1c** (Cl)		toluene	61	93 (69% ee)	:	7
6	**1a** (Br)		toluene	84	**94** (**89%** ee)	:	6
7	**1c** (Br)		toluene	71	94 (50% ee)	:	6
8	**1a** (Br)		toluene	89	**97** (**87%** ee)	:	3
9	**1c** (Br)		toluene	80	96 (60% ee)	:	4
10	**1a** (Br)		toluene	63	**94** (**61%** ee)	:	6
11	**1c** (Br)		toluene	56	95 (2% ee)	:	5

[a] All reactions were carried out 0.1 mmol (10 mol% based on **3**) of **1**, 1.0 mmol of **3**, and 1.3 mmol of **2** in the presence of MS 4A, unless otherwise marked. [b] 0.2 mmol (20 mol% based on **3**) of **1** was employed.

Inspection of Table 1 reveals characteristic features of the present diastereo- and enantioselective glyoxylate-ene reaction. The enantioselectivity is highly dependent on the chiral titanium complex (**1**) employed. Of particular interest is that the remarkably enhanced level of enantioselectivity is obtained with the 6-Br-BINOL-Ti catalysts (**1a**) (entries 1, 3, 6, 8, and 10), particularly in less polar solvent, toluene (entry 1 *vs.* 3). The marked solvent effect on

enantioselectivity observed for the 6-Br-BINOL-Ti catalyst (**1a**) is in contrast to the little solvent effect observed for the BINOL-Ti catalyst (**1c**) (entry 2 *vs.* 5). Significantly, the chiral titanium complexes (**1a**) lead to the predominant formation of *syn*-α-hydroxy-β-methyl esters (**4**) in high enantioselectivity except for the reaction with 2-methyl-2-butene (61% ee). The remarkable enhancement of enantioselectivity is presumably due to the effective shielding over the enantioface of glyoxylate by the halide ligands through the compression of internal bond angle X-Ti-X.[8] Unfortunately, the chiral titanium complex (**1b**) derived from binaphthyl ditrifylamine, though expected to direct the enantiofacial selective attack of ene components to glyoxylate by the sterically demanding trifylamine moiety, provides disappointingly low level of asymmetic induction (entry 4).

In summary, we have disclosed herein the designed binaphthyl-derived chiral titanium complex (**1a**) as a new type of efficient catalyst for *syn*-diastereoselective and enantioselective glyoxylate-ene reactions. The key to success is the modification at the 6 position of binaphthol by electron withdrawing group, bromide, in controlling the conformation of binaphthyl rings. Further work along this line is now under investigation.[9]

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2. Review on carbonyl-ene reactions: Mikami, K.; Shimizu, M. *Chem. Rev.* **1992**, *92*, 1021.
3. (a) Mikami, K.; Terada, M.; Nakai, T. *J. Am. Chem. Soc.* **1990**, *112*, 3949; *Ibid.* **1989**, *111*, 1940. (b) Mikami, K.; Terada, M.; Narisawa, S.; Nakai, T. *Org. Synth.* **1992**, *71*, 14.
4. 98% ee of (*R*)-6,6'-dibromo-1,1'-bi-2-naphthol was used as a chiral ligand. The enantiomeric purity was determined by chiral HPLC analysis: t_R of (*R*)-isomer 14.3 min and (*S*)-isomer 11.9 min (Daicel CHIRALPAK AS, eluent, hexane/ isopropanol = 3:1, flow rate 0.5 mL/min, detection 254-nm light); $[\alpha]_D^{29}$ -52.3 ° (c 1.15, THF).
5. Methyl 3-(1-cyclohexenyl)-2-hydroxybutanoate: *syn*-isomer: ^{1}H NMR ($CDCl_3$) δ 1.02 (d, *J* = 7.1 Hz, 3H), 1.5 - 1.7 (m, 4H), 1.9 - 2.1 (m, 4H), 2.43 (m, 1H), 2.56 (d, *J* = 6.4 Hz, 1H), 3.77 (s, 3H), 4.22 (dd, *J* = 4.5, 6.4 Hz, 1H), 5.53 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 12.7, 22.4, 22.9, 25.3,

26.7, 45.1, 52.3, 73.2, 123.3, 138.1, 175.4. *anti*-isomer: ^{1}H NMR ($CDCl_3$) δ 1.11 (d, J = 7.2 Hz, 3H), 1.5 - 1.7 (m, 4H), 1.9 - 2.1 (m, 4H), 2.49 (m, 1H), 2.51 (d, J = 6.8 Hz, 1H), 3.76 (s, 3H), 4.09 (dd, J = 5.6, 6.8 Hz, 1H), 5.53 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 15.5, 22.4, 22.9, 25.3, 26.5, 45.4, 52.1, 74.0, 124.8, 137.5, 175.0. Methyl 3-(1-cycloheptenyl)-2-hydroxybutanoate: *syn*-isomer: ^{1}H NMR ($CDCl_3$) δ 1.00 (d, J = 7.0 Hz, 3H), 1.4 - 1.8 (m, 6H), 2.1 - 2.2 (m, 4H), 2.49 (m, 1H), 2.50 (d, J = 6.3 Hz, 1H), 3.77 (s, 3H), 4.18 (dd, J = 4.5, 6.3 Hz, 1H), 5.66 (t, J = 6.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 13.0, 27.0, 27.2, 28.5, 31.3, 32.9, 46.8, 52.3, 72.8, 128.3, 144.6, 174.9. *anti*-isomer: ^{1}H NMR ($CDCl_3$) δ 1.10 (d, J = 7.1 Hz, 3H), 1.4 - 1.8 (m, 6H), 2.1 - 2.2 (m, 4H), 2.45 (m, 1H), 2.46 (d, J = 6.1 Hz, 1H), 3.76 (s, 3H), 4.06 (dd, J = 5.1, 6.1 Hz, 1H), 5.66 (t, J = 6.2 Hz, 1H). Methyl 2-hydroxy-3,4-dimethyl-4-pentenoate: *syn*-isomer: ^{1}H NMR ($CDCl_3$) δ 1.01 (d, J = 7.0 Hz, 3H), 1.79 (bs, 3H), 2.57 (m, 1H), 2.65 (d, J = 5.8 Hz, 1H), 3.77 (s, 3H), 4.26 (dd, J = 3.9, 5.8 Hz, 1H), 4.82 (bs, 1H), 4.88 (bs, 1H); ^{13}C NMR ($CDCl_3$) δ 12.7, 21.1, 44.3, 52.5, 72.9, 112.4, 146.3, 175.4. *anti*-isomer: ^{1}H NMR ($CDCl_3$) δ 1.15 (d, J = 7.2 Hz, 3H), 1.71 (bs, 3H), 2.57 (m, 1H), 2.62 (d, J = 6.5 Hz, 1H), 3.76 (s, 3H), 4.10 (dd, J = 5.5, 6.5 Hz, 1H), 4.78 (bs, 1H), 4.86 (bs, 1H); ^{13}C NMR ($CDCl_3$) δ 15.7, 20.6, 45.0, 52.4, 74.1, 113.4, 145.7, 175.1.

6. The relative stereochemistry was assigned by the similarity seen in the ^{1}H NMR spectra to those reported by Snider *et. al.* Snider, B. B.; Straten, J. W. *J. Org. Chem.* **1979**, *44*, 3567.
7. Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512.
8. The 6-Br-BINOL-Ti catalyst (**1a**) is also effective for the reaction with 1,1-disubstituted olefins to provide higher enantioselectivity than that in the BINOL-Ti (**1c**) catalyzed reaction.
9. The glyoxylate-ene reaction with vinylsulfides and -selenides as alternatives to mono- and 1,2-disubstituted olefins catalyzed by **1c** provides diastereomeric ene products with a moderate to excellent level of enantioselectivity. Terada, M.; Matsukawa, S.; Mikami, K. *J. Chem. Soc., Chem. Commun.* **1993**, 327. Also see: Mikami, K.; Matsukawa, S. *J. Am. Chem. Soc.* **1993**, *115*, 7039.

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