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Asymmetric Carbonyl Addition Reactions to Benzyloxyaldehydes by Binaphthol-Titanium Catalyst: *Anti- vs. Syn*-Diastereofacial Preference in Anomalous Nonchelation Complexation

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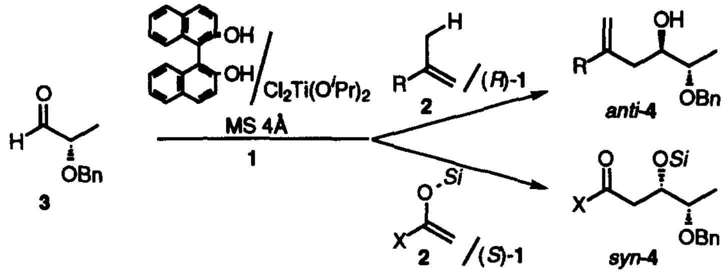
Abstract: *An anomalous nonchelation diastereofacial selectivity is observed in the titanium-catalyzed carbonyl addition reaction to benzyl-protected alkoxyaldehydes. There is a dichotomy in the sense of syn- vs. anti-diastereofacial preference, dictated by the bulkiness of the migratory group: The sterically demanding silyl group gives syn-diastereofacial preference and the less sterically demanding proton leads to anti-diastereofacial preference.* © 1997 Elsevier Science Ltd. All rights reserved.

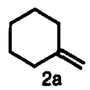
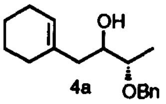
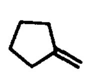
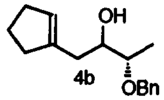
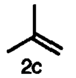
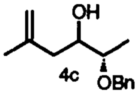
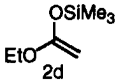
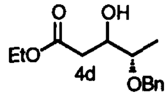
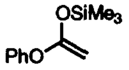
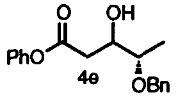
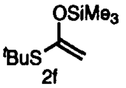
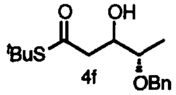
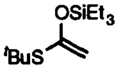
There is the "central dogma" in the asymmetric aldol and other carbonyl addition reactions with chiral hydroxyaldehydes: Chelation occurs with the benzyl protecting group and nonchelation results with the silyl protecting group.[1] We report here an "antithesis" to the central dogma, namely an anomalous sense of nonchelation selection with the benzyl-protected hydroxyaldehydes (Scheme 1, Table 1), in the asymmetric carbonyl addition reactions catalyzed by a binaphthol-derived chiral titanium complex (BINOL-Ti: **1**).[2] Furthermore, there is a dichotomy in the sense of *anti- vs. syn*-diastereofacial preference in the nonchelation-controlled carbonyl-ene and aldol type reactions, respectively.

Scheme 1



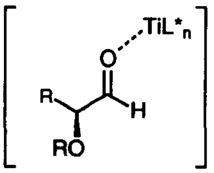
First, a high level of *anti*-diastereofacial selectivity is observed in carbonyl-ene reactions[3] with (*S*)-α-benzyloxypropanal (**3**) catalyzed by (*R*)-BINOL-Ti complex **1** (entries 1, 3 and 4).[4] The *anti*-diastereofacial selectivity[5] is in sharp contrast to the usual *syn*-selectivity obtained with closely related achiral titanium complexes such as di(*i*-propoxy)titanium dichloride and tri(*i*-propoxy)titanium chloride (entries 6 and 7). The (*S*)-catalyst provides the *syn*-diastereomer, but with lower selectivity and in lower chemical yield (entries 2 and 5), indicating that the (*S*)-aldehyde **3** and (*S*)-catalyst are the mis-matched pair for the ene reaction. The *anti*-preference in the matched pair suggests that the present ene reaction proceeds via the nonchelated complex with the bulky BINOL-Ti catalyst (**A**).[6] In sharp contrast, the aldol type reaction[4,7] of (*S*)-**3** catalyzed by (*S*)-**1** gives high levels of *syn*-diastereofacial selectivity (entries 9, 11 and 13),[8] while lower levels of *anti*-selectivity are observed with the (*R*)-catalyst (entries 8, 10 and 12), indicating that the (*S*)-aldehyde **3** and (*S*)-catalyst **1** are the matched pair in the aldol reaction.

Table 1. Diastereofacial Selectivity in Ene and Aldol Reactions [a]

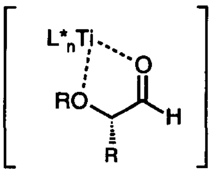
entry	2	1	yield (%)	4 (product)	*syn* / *anti*[b]
1	 2a	*R*	38	 4a	<1 : >99
2		*S*	10		84 : 16
3	 2b	*R*	55	 4b	<1 : >99
4	 2c	*R*	24	 4c	<1 : >99
5		*S*	7		84 : 16
6		$(i\text{-PrO})_2TiCl_2$	60		87 : 13
7		$(i\text{-PrO})_3TiCl$	48		91 : 9
8	 2d	*R*	71	 4d	17 : 83
9		*S*	73		98 : 2
10	 2e	*R*	45	 4e	18 : 82
11		*S*	65		97 : 3
12	 2f	*R*	61	 4f	18 : 82
13		*S*	68		97 : 3
14	 2g	*S*	66		98 : 2

[a] Conditions as in Ref 4. [b] The isomeric ratio was determined by capillary GC and/or HPLC analysis.

Syn-diastereofacial selectivity[9] is observed in the aldol reaction with (*S*)-(*t*-butyldimethyl)siloxypropanal **5**,[10] which proceeds via nonchelation complex (Scheme 2). Thus, the aldol reactions with the benzyloxyaldehyde also involve the nonchelated complex (**A**) leading to the *syn*-preference, rather than the chelated complex (**B**) to uncover the opposite π-face[11].



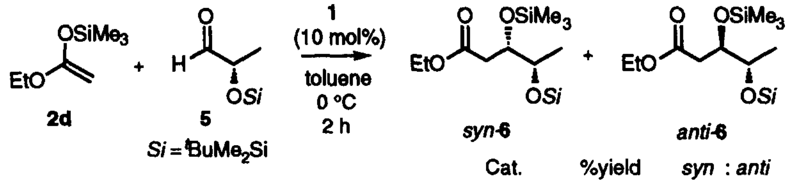
A



B

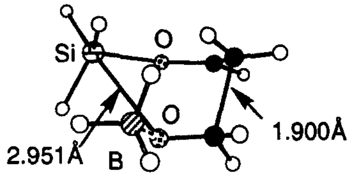
Not only carbonyl-ene but also aldol ("silatropic-ene")[12] reactions would proceed via cyclic transition states (TSs). Indeed, *ab initio* calculations (RHF/6-31G*) provided the cyclic (boat **C** and chair **D**) TSs for the BH_3-promoted aldol reaction of trihydrosilyl enol ether of acetaldehyde with formaldehyde. Thus, the *anti*-diastereoselectivity in carbonyl-ene reactions is exemplified by the Felkin-Anh-like[13] cyclic TS model (T_1).

Scheme 2

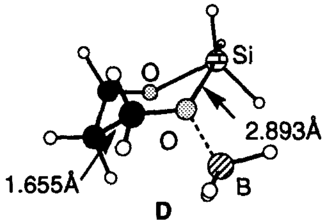


Cat.	%yield	*syn* : *anti*
(*R*)-1	47	64 : 36
(*S*)-1	48	85 : 15

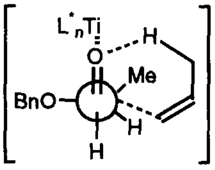
In the aldol reaction, by contrast, the inside-crowded TS (**T$_1$'**) is less favorable than **T$_2$'**. Because of the steric repulsion between the trimethylsilyl group and the inside methyl group of aldehyde (**T$_1$'**), *syn*-diastereofacial selectivity is visualized by the *anti*-Felkin-like cyclic TS model (**T$_2$'**). As expected, the use of a sterically more demanding triethylsilyl group resulted in the increase in the *syn* selectivity, though slightly (Table 1, entries 13 vs. 14). Furthermore, the aldol reaction of (*S*)-**3** and enoxysilacyclobutane **7**, which has been reported to proceed through a tight cyclic TS in the absence of the Lewis acid catalysis,[14] shows a higher level of *syn* selectivity by the catalysis of (*S*)-**1** (Scheme 3).



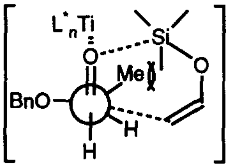
C



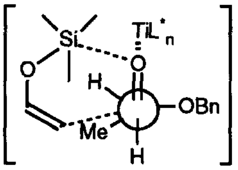
D



T1

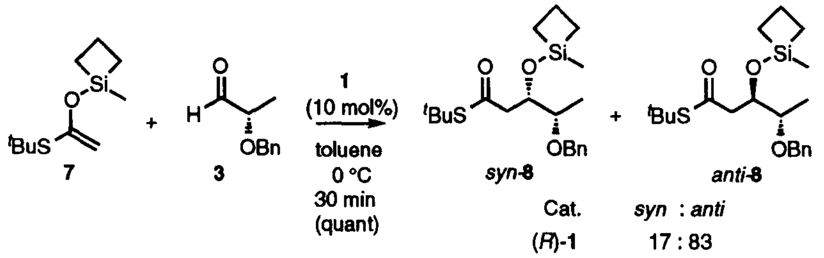


T1'



T2'

Scheme 3



Cat.	*syn* : *anti*
(*R*)-1	17 : 83
(*S*)-1	98 : 2

In summary, we have disclosed the anomalous nonchelation diastereofacial selectivity in the titanium-catalyzed carbonyl addition reaction to benzyl-protected alkoxyaldehydes. Furthermore, there is a dichotomy in the sense of *syn*- *vs*. *anti*-diastereofacial preference,[15] dictated by the bulkiness of the migratory group.

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6 A similarly high (>99%) level of *anti*-diastereofacial selectivity was obtained in the ene reactions of (*S*)-**3** with 1 or 2 equivalents of (*R*)-**1**.

7 (a) Review: Mukaiyama, T. *Org. React.* **1982**, *28*, 203-331. Asymmetric catalytic reactions: (b) Kobayashi, S.; Uchiro, H.; Fujishita, Y.; Shiina, I.; Mukaiyama, T. *J. Am. Chem. Soc.* **1991**, *113*, 4247-4252. (c) Parmee, E. R.; Tempkin, O.; Masamune, S.; Abiko, A. *J. Am. Chem. Soc.* **1991**, *113*, 9365-9366. (d) Furuta, K.; Maruyama, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1991**, *113*, 1041-1042. (e) Kiyooka, S.; Kaneko, Y.; Komura, M.; Matsuo, H.; Nakano, M. *J. Org. Chem.* **1991**, *56*, 2276-2278. (f) Corey, E. J.; Cywin, C. L.; Roper, T. D. *Tetrahedron Lett.* **1992**, *33*, 6907-6910. (g) Mikami, K.; Matsukawa, S. *J. Am. Chem. Soc.* **1993**, *115*, 7039-7040. (h) Carreira, E. M.; Singer, R. A.; Lee, W. *J. Am. Chem. Soc.* **1994**, *116*, 8837-8838. (i) Keck, G. E.; Krishnamurthy, D. *J. Am. Chem. Soc.* **1995**, *117*, 2363-2364.

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