

Bis((*S,S*)-binaphthoxy)(isopropoxy)titanium Oxide as a μ -Oxo-Type Chiral Lewis Acid: Application to Catalytic Asymmetric Allylation of Aldehydes

Hideo Hanawa, Takuya Hashimoto, and Keiji Maruoka*

Department of Chemistry, Graduate School of Science, Kyoto University, Sakyo, Kyoto 606-8502, Japan

Received March 4, 2002; E-mail: maruoka@kuchem.kyoto-u.ac.jp

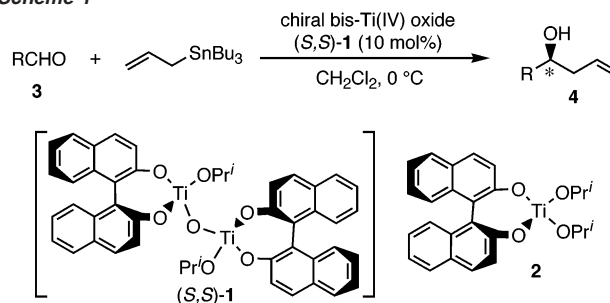
Catalytic asymmetric synthesis in the efficient production of enantiomerically rich compounds is of considerable current interest in organic synthesis, and hence a number of chiral metal catalysts possessing various chiral auxiliaries have been devised to a useful level in recent years.¹ The development of efficient enantioselective methods by the utilization of new chiral metal catalysts increasingly requires the rational design of new reagents and processes. In this regard, we recently communicated that the Al–O–Al unit in MAO (methylalumoxane) and bis(dimethylaluminum) oxide as effective Lewis acids is crucially important for the strong activation of carbonyl and epoxide oxygens.² This observation prompted us to design a new, chiral Lewis acid possessing the key M–O–M unit (M: metal) including a certain chiral auxiliary. Accordingly, we prepared a new, binaphthyl-modified bis-Ti(IV) oxide of type **1** for the enantioselective activation of carbonyl moieties (Scheme 1). The reactivity and the chiral efficiency of bis-Ti(IV) oxide (*S,S*)-**1** as a chiral Lewis acid was examined by doing the catalytic asymmetric allylation of aldehydes with diallyltributyltin in comparison with (*S*)-binaphthoxytitanium diisopropoxide (**2**) as a corresponding mono-Ti(IV) Lewis acid.³

The requisite bis-Ti(IV) oxide (*S,S*)-**1** was synthesized by two different routes [A] and [B] starting from triisopropoxytitanium chloride, (PrⁱO)₃TiCl as shown in Scheme 2.⁴ Positive ESI-MS clearly showed an *m/z* peak at 943 (M•2THF + H⁺), indicating the formation of (*S,S*)-**1**•2THF coordination complex by comparison with the theoretical molecular ion peak. Reaction of hydrocinnamaldehyde **3** (R = CH₂CH₂Ph) with allyltributyltin (1.1 equiv) under the influence of in situ generated chiral bis-Ti(IV) oxide (*S,S*)-**1** (10 mol %) [prepared by method A] in CH₂Cl₂ at 0 °C for 4 h afforded 1-phenyl-5-hexen-3-ol **4** (R = CH₂CH₂Ph) in 84% yield with 99% ee.⁵ Notably, both the reaction rate and the enantioselectivity of the allylation are much lowered (e.g., 10% yield and 72% ee for hydrocinnamaldehyde) under similar reaction conditions with a chiral mono-Ti(IV) catalyst **2** (20 mol %).⁶ Alternatively, chiral bis-Ti(IV) oxide (*S,S*)-**1**, prepared by method B,^{7,8} exhibited similar reactivity and enantioselectivity (81% yield with 98% ee) compared to the catalyst by method A.⁵

Other selected examples are listed in Table 1. Several characteristic features of the present allylation follow: (1) The chiral bis-Ti(IV) oxide (*S,S*)-**1** exhibits uniformly high asymmetric induction as well as high chemical yield. (2) The use of Ti–O–Ti unit in the chiral bis-Ti(IV) catalyst (*S,S*)-**1** toward aldehyde carbonyls strongly accelerates the rate of allylation compared to the corresponding mono-Ti(IV) catalyst **2** (entries 5 and 8). (3) The enantioselectivity of the present allylation is not sensitive to the reaction temperature (entries 1 vs 2 and 10 vs 11). (4) The amount of chiral bis-Ti(IV) oxide (*S,S*)-**1** can be reduced to 5 mol % without affecting the enantioselectivity (entries 3, 6, and 12).

We also carried out the asymmetric allylation by using nonracemic bis-Ti(IV) oxide **1** (by method C) with partially resolved (*S*)-binaphthol as chiral auxiliary, which includes a mixture of (*S,S*)-

Scheme 1



Scheme 2

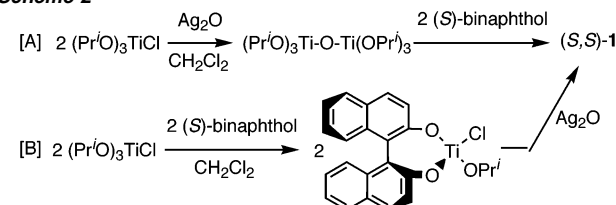


Table 1. Asymmetric Allylation of Aldehydes by Chiral Bis-Ti(IV) Oxide **1**^a

entry	aldehyde	Ti catalyst (mol %)	time (h)	% yield ^b	% ee ^c (config) ^d
1	PhCH ₂ CH ₂ CHO	1 (10)	4	84	99 (<i>R</i>)
2		1 (10) ^e	16	82	98 (<i>R</i>)
3		1 (5)	12 [7] ^f	77 [95]	98 [98] (<i>R</i>)
4	CH ₃ (CH ₂) ₆ CHO	1 (10)	12	85	99 (<i>R</i>) ^g
5		2 (20)	12	14	81 (<i>R</i>) ^g
6		1 (5)	24 [12] ^f	86 [92]	99 [98] (<i>R</i>) ^g
7	(CH ₃) ₂ CHCHO	1 (10)	28 [18] ^f	71 [91]	>99 [99] (<i>S</i>) ^h
8		2 (20)	28	7	85 (<i>S</i>) ^h
9	PhCH=CHCHO	1 (10)	15	70	95 (<i>S</i>)
10	PhCHO	1 (10)	7	90	96 (<i>S</i>)
11		1 (10) ^e	24	81	96 (<i>S</i>)
12		1 (5)	[9] ^f	[94]	[97] (<i>S</i>)
13	<i>p</i> -bromobenzaldehyde	1 (10)	15	85	98 (<i>S</i>)
14	furfural	1 (10)	18	96	97 (<i>S</i>)

^a Unless otherwise noted, the reaction of aldehyde and allyltributyltin (1.1 equiv) was carried out in the presence of chiral bis-Ti(IV) oxide **1** (by method A) or chiral mono-Ti(IV) **2** in CH₂Cl₂ at 0 °C. ^b Isolated yield.

^c Determined by HPLC analysis using Chiralcel OD and OJ. ^d Determined by comparison of the sign of optical rotation with reported values. See ref 3p. ^e At –15 °C. ^f Use of 2 equiv of allyltributyltin. ^g Determined by GC analysis using a chiral column (Chrompack CP-CHIRASIL-DEX CB).

^h Determined by chiral GC analysis after conversion to its benzoate.

1, (*S,R*)-**1**, and minor (*R,R*)-**1**. Selected results are summarized in Table 2, which clearly shows a positive nonlinear effect in correlating the enantiopurity of allylation product **4** (R = CH₂CH₂-Ph) with the ee of (*S*)-binaphthol.^{3g} In marked contrast, however, starting from optically pure (*S*)- and (*R*)-binaphthol, optically pure bis-Ti(IV) oxides, (*S,S*)-**1** and (*R,R*)-**1** were prepared independently, and asymmetric allylation by mixing of such (*S,S*)-**1** and (*R,R*)-**1** (by method D) gave rise to product **4** (R = CH₂CH₂Ph) in rather

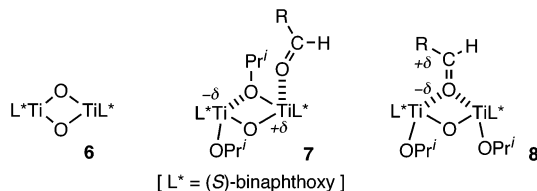
Table 2. Chiral Amplification in Asymmetric Allylation Catalyzed by Nonracemic Bis-Ti(IV) Oxide **1**^a

% ee of 1 ^b	method C ^c		method D ^c	
	% yield	% ee ^d	% yield	% ee ^d
0	38	0	70	3
25	50	64	74	23
50	63	87	75	52
75	69	96	75	75
100	84	99	84	99

^a Reaction of aldehyde **3** (R = CH₂CH₂Ph) and allyltributyltin (1.1 equiv) was carried out in the presence of nonracemic bis-Ti(IV) oxide **1** (10 mol %) in CH₂Cl₂ (0.033 M) at 0 °C for 4 h. ^b In the nonracemic binaphthol, (*S*)-binaphthol was in excess. ^c For methods C and D, see text. ^d Determined by HPLC analysis using Chiralcel OD.

high yield without any chiral amplification. These results imply the following important points: (1) symmetric (*S,S*)-**1** and (*R,R*)-**1** are more reactive than *meso* (*S,R*)-**1** catalyst; (2) bis-Ti(IV) oxide **1** exists as a monomeric species rather than dimeric species in solution;⁹ (3) bis-Ti(IV) oxide **1** is coordinatively stable, and no scrambling was observed between (*S,S*)-**1** and (*R,R*)-**1** under the reaction conditions.

Several possible reaction pathways have been considered to account for the activation phenomenon with chiral bis-Ti(IV) oxide **1**.¹⁰ First, chiral bis-Ti(IV) oxide **1** might not exist as an equilibrium mixture of ((*S*)-binaphthoxy)Ti=O (**5**)¹¹ and (*S*)-binaphthoxytitanium diisopropoxide (**2**).⁶ It should be noted that (*S*)-binaphthoxytitanium μ -oxo complex **6** showed only low reactivity and selectivity under similar allylation condition.¹² In addition, Keck's mono-Ti(IV) reagent derived from Ti(OPr^{*i*})₄ and (*S*)-binaphthol (2 equiv) was not generated by method A or B.^{3d} Therefore, the high reactivity and selectivity of the chiral bis-Ti(IV) oxide **1** might be ascribed to the intramolecular coordination of one isopropoxy oxygen to the other titanium intramolecularly, thereby enhancing the otherwise weak Lewis acidity of the original Ti(IV) center for the carbonyl activation as shown in **7**. Alternatively, a carbonyl oxygen coordinates simultaneously to two Ti centers as an intermediate or as a dynamic species, thereby allowing the strong activation of such an aldehyde carbonyl as depicted in **8**. Although the elucidation of the most plausible reaction mechanism involving chiral bis-Ti(IV) catalyst **1** must await further research, the present asymmetric approach provides a very useful way for obtaining high reactivity and selectivity by the simple introduction of the M–O–M unit in the design of chiral Lewis acid catalysts.



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Supporting Information Available: Representative experimental procedures (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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