Catalytic Asymmetric Allylation of Aldehydes and Related Reactions with Bis(((*S*)-binaphthoxy)(isopropoxy)titanium) Oxide as a μ-Oxo-Type Chiral Lewis Acid

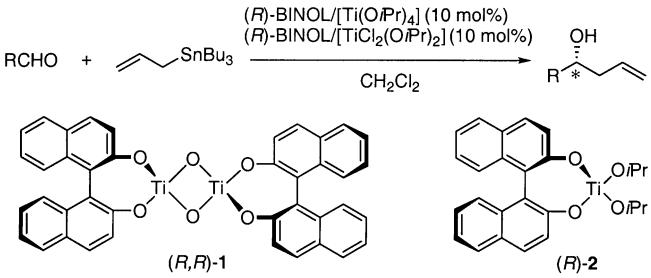
Hideo Hanawa, Daisuke Uraguchi, Shunsuke Konishi, Takuya Hashimoto, and Keiji Maruoka*[a]

Abstract: A new, chiral bis-Ti^{IV} oxide of type **3** has been designed and can be utilized for strong activation of aldehyde carbonyls, thereby allowing a new catalytic enantioselective allylation of aldehydes with allyltributyltin. The chiral bis-Ti^{IV} catalyst (*S*,*S*)-**3** can be readily prepared either by treatment of bis(triisopropoxy)titanium oxide with (*S*)-BINOL or by treatment of ((*S*)-binaphthoxy)isopropoxytitanium chloride with silver(I) oxide. Treatment of hydrocinnamaldehyde with allyltributyltin under the influence of chiral bis-Ti^{IV} oxide (*S*,*S*)-**3** generated in situ (10 mol%) in CH_2Cl_2 afforded an allylation product in 84% yield and with 99% *ee*. This asymmetric allylation with non-racemic bis-Ti^{IV} oxide **3** and partially resolved (*S*)-BINOL shows a positive nonlinear effect in correlation of the enantiopurity of the allylation product with the *ee* of the (*S*)-BINOL. Chiral bis-Ti^{IV} oxide (*S*,*S*)-**3** can also be utilized for related reactions such as asymmetric methallylation and propargylation of aldehydes with high enantioselectivity. This asymmetric approach provides a very useful way of obtaining high reactivity and selectivity through the simple introduction of the M–O–M unit into the design of chiral Lewis acid catalysts.

Keywords: aldehydes · allylation · asymmetric synthesis · Lewis acids · titanium

Introduction

Asymmetric allylation of carbonyl compounds is currently an important transformation in asymmetric synthesis, and a number of chiral Lewis acids possessing various chiral auxiliaries, in combination with allylsilane or allyltin compounds, have been elaborated for this purpose.[1] Among these, BINOL/Ti^{IV} complexes have been most extensively studied as effective chiral Lewis acid catalysts in view of several characteristics, including: 1) the commercial availability of both optically pure BINOL and Ti^{IV} compounds, 2) the easy generation of these Ti^{IV} complexes, and 3) their versatility and general applicability in terms of substrates and allylmetal compounds.[2] Indeed, catalytic asymmetric allylation of aldehydes and allyltributyltin can be effected by use of BINOL/[Ti(O*i*Pr)$_4$] or BINOL/[$TiCl_2$(O*i*Pr)$_2$] complexes (Scheme 1), although the nature of these useful chiral catalysts remains elusive.[3] By mixing (*R*)-BINOL and [$TiCl_2$(O*i*Pr)$_2$] in the presence of molecular sieves (4 Å) the chiral Ti^{IV} μ-oxo complex (*R*,*R*)-**1** was obtained accidentally, and shown to be an efficient catalyst for the glyoxylate–ene reaction.[4] In addition, Mikami and Corey disclosed that



Scheme 1. Asymmetric allylation of aldehydes with chiral (*R*)-BINOL/Ti^{IV} complexes.

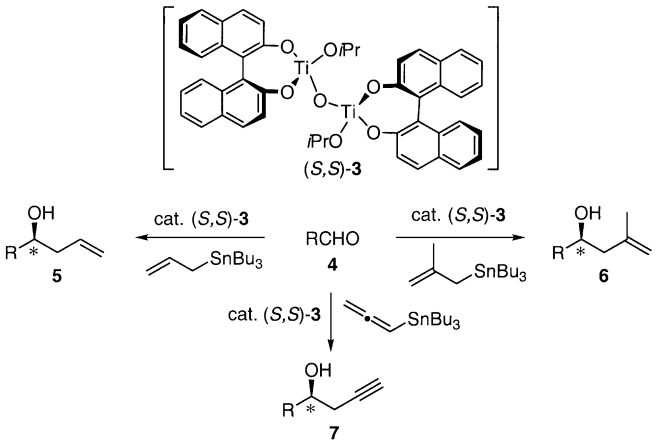
active catalysts, obtained by treatment of [((*R*)-binaphthoxy)-Ti(O*i*Pr)$_2$] ((*R*)-**2**) with hydrated molecular sieves (4 Å), might be chiral Ti^{IV} μ-oxo clusters for effecting asymmetric ene and Diels–Alder reactions.[5] Other chiral Ti^{IV} μ-oxo clusters were also prepared by hydrolysis of (*R*)-**2**.[6] In this context, we are interested in investigating the reactivity and enantioselectivity of certain structurally defined, chiral Ti^{IV} μ-oxo complexes for the activation of the carbonyl moiety.

Recently we reported that the Al–O–Al unit in MAO (methylalumoxane) and bis(dimethylaluminium) oxide, as effective Lewis acids, is crucially important for the strong activation of carbonyl and epoxide oxygens.[7] This observation led us to design a new, chiral Ti^{IV} Lewis acid possessing the key M–O–M unit (M: metal) including a particular chiral

[a] Prof. K. Maruoka, H. Hanawa, D. Uraguchi, S. Konishi, T. Hashimoto
Department of Chemistry, Graduate School of Science
Kyoto University, Kyoto 606-8502 (Japan)
Fax: (+81) 75-753-4041
E-mail: maruoka@kuchem.kyoto-u.ac.jp

 DOI: 10.1002/chem.200305078 © 2003 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

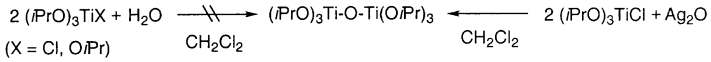
auxiliary. Accordingly, we prepared a new, binaphthoxyl-modified bis-Ti^{IV} oxide of type **3** for the enantioselective activation of carbonyl moieties. The reactivity and the chiral efficiency of bis-Ti^{IV} oxide (*S*,*S*)-**3** as a chiral Lewis acid were examined by the use of the catalytic asymmetric allylation of aldehydes with allyltributyltin, together with the analogous methallylation and propargylation reactions (Scheme 2).[8]



Scheme 2. Asymmetric transformation of aldehydes with chiral bis-Ti^{IV} oxide (*S*,*S*)-**3**.

Results and Discussion

Preparation of mono-μ-oxo-type chiral bis-Ti^{IV} complexes: We first attempted to synthesize the requisite mono-μ-oxo Ti–O–Ti structure by simple hydrolysis of triisopropoxytitanium chloride [(*i*PrO)$_3$TiCl] or titanium(IV) tetraisopropoxide [Ti(O*i*Pr)$_4$], which gave several reaction products.[9] However, treatment of (*i*PrO)$_3$TiCl (2 equiv.) with Ag_2O (1 equiv) in CH_2Cl_2 at room temperature (Scheme 3) with vigorous



Scheme 3. Production of bis(triisopropoxytitanium) oxide (*i*PrO)$_3$Ti–O–Ti(O*i*Pr)$_3$.

stirring and with exclusion of direct light resulted in clean formation of bis(triisopropoxytitanium) oxide (*i*PrO)$_3$Ti–O–Ti(O*i*Pr)$_3$.[10]

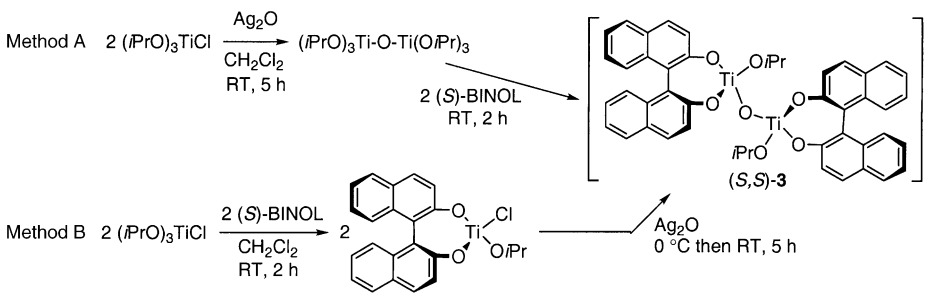
With this information to hand, the requisite binaphthoxy-modified bis-Ti^{IV} oxide (*S*,*S*)-**3** was prepared by initial treatment of [(*i*PrO)$_3$TiCl] with Ag_2O as described above, and subsequent addition of (*S*)-BINOL (Scheme 4; Method A). The same bis-Ti^{IV} oxide (*S*,*S*)-**3** was also synthesized by treatment of [(*i*PrO)$_3$TiCl] with (*S*)-BINOL (2 equiv) in CH_2Cl_2 and subsequently with Ag_2O (Method B).[11] Positive ESI-MS clearly showed an *m*/*z* peak at 943 ([*M*·2THF+H]$^+$), indicating the formation of the (*S*,*S*)-**3**·2THF coordination complex by comparison with the theoretical molecular ion peak.[12]

In addition, the formation of the Ti–O–Ti unit by Methods A and B was confirmed by treatment of *cis*-[TiCl$_2$(η^2-guaiacolato)$_2$] (2 equiv) with Ag_2O (1 equiv) in CH_2Cl_2 to furnish [Ti$_2$(μ-O)Cl$_2$(η^2-guaiacolato)$_4$] **8**, which is spectroscopically identical with that produced by the reported procedure with use of H_2O (Scheme 5).[13] Thus, the Ag_2O-mediated approach seems to provide a simple, yet reliable method for the controllable formation of the desired mono-μ-oxo Ti–O–Ti bridge.[9f]

Catalytic asymmetric allylation of aldehydes with chiral bis-Ti^{IV} oxides: Treatment of hydrocinnamaldehyde **4** (R = CH_2CH_2Ph) with allyltributyltin (1.1 equiv) under the influence of chiral bis-Ti^{IV} oxide (*S*,*S*)-**3** generated in situ (10 mol %) [prepared by Method A] in CH_2Cl_2 at 0 °C for 4 h afforded 1-phenyl-5-hexen-3-ol (**5**, R = CH_2CH_2Ph) in 84 % yield and with 99 % *ee* (see Scheme 2). The absolute configuration of the homoallylic alcohol was determined to be *R* by correlation to the authentic sample.[2b] The catalyst loading can be reduced to 5 mol % with some reduction in the chemical yield, which is improved by use of excess allyltributyltin (2 equiv). It should be noted that both the reaction rate and the enantioselectivity of the allylation are greatly lowered (e.g., 10 % yield and 72 % *ee* for hydrocinnamaldehyde) under similar reaction conditions with a chiral mono-Ti^{IV} catalyst (*S*)-**2** (20 mol %).[14] Alternatively, chiral bis-Ti^{IV} oxide (*S*,*S*)-**3**, prepared by Method B, exhibited reactivity and enantioselectivity (81 % yield with 98 % *ee*) similar to that of the catalyst prepared by Method A. Similar results were obtained when using the supernatant solution of the chiral bis-Ti^{IV} oxide **3** prepared by Method A or B after removal of the precipitated AgCl. Moreover, attempted addition of AgCl to chiral mono-Ti^{IV} catalyst (*S*)-**2** also afforded a result comparable to those described above. Other examples are listed in Table 1.

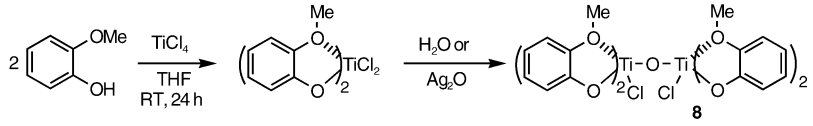
Several characteristic features of this allylation follow:

1) The chiral bis-Ti^{IV} oxide (*S*,*S*)-**3** exhibits uniformly high asymmetric induction as well as high chemical yields.
2) The incorporation of a mono-μ-oxo Ti–O–Ti unit in the chiral bis-Ti^{IV} catalyst (*S*,*S*)-**3** strongly accelerates the rate of allylation of aldehyde carbonyls relative to the corresponding mono^{IV} catalyst (*R*)-**2** (Table 1, entries 6 and 8).



Scheme 4. Preparation of chiral bis-Ti^{IV} oxide (*S*,*S*)-**3** by methods A or B.

© 2003 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim



Scheme 5. Preparation of $[Ti_2(\mu\text{-}O)Cl_2(\eta^2\text{-guaiacolato})_4]$ (**8**).

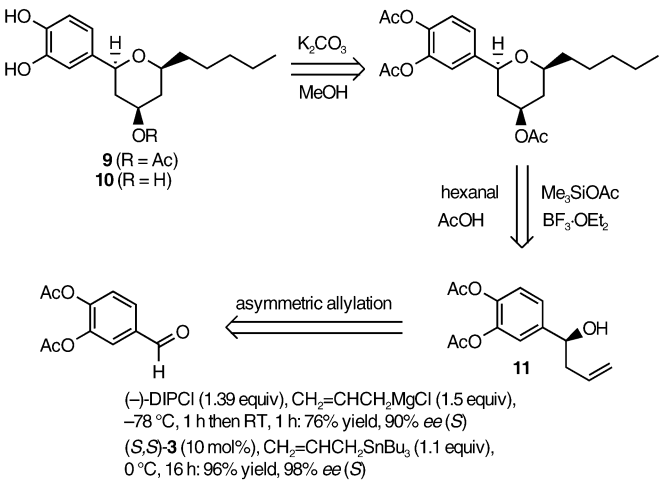
Table 1. Asymmetric allylation of aldehydes with allyltributyltin catalyzed by chiral bis-Ti^{IV} oxide (*S*,*S*)-**3**.[a]

	Aldehyde	Ti catalyst [mol %][b]	Reaction time [h]	Yield [%]	*ee* [%][c] (config)[d]
1	$PhCH_2CH_2CHO$	(*S*,*S*)-**3** (10)	4	84	99 (*R*)
2		(*S*,*S*)-**3** (10)[e]	4	81	98 (*R*)
3		(*S*,*S*)-**3** (10)	16[f]	82	98 (*R*)
4		(*S*,*S*)-**3** (5)	12	77	98 (*R*)
5		(*S*,*S*)-**3** (5)	7[g]	95	98 (*R*)
6		(*S*)-**2** (20)	4	10	72 (*R*)
7	$CH_3(CH_2)_6CHO$	(*S*,*S*)-**3** (10)	12	85	99 (*R*)[h]
8		(*S*)-**2** (20)	12	14	81 (*R*)[h]
9		(*S*,*S*)-**3** (5)	24	86	99 (*R*)[h]
10		(*S*,*S*)-**3** (5)	12[g]	92	98 (*R*)[h]
11	$(CH_3)_2CHCHO$	(*S*,*S*)-**3** (10)	28	71	> 99 (*S*)[i]
12		(*S*)-**2** (20)	28	7	85 (*S*)[i]
13		(*S*,*S*)-**3** (10)	18[g]	91	99 (*S*)[i]
14	PhCH=CHCHO	(*S*,*S*)-**3** (10)	15	70	95 (*S*)
15		(*S*)-**2** (20)	15	10	83 (*S*)
16	PhCHO	(*S*,*S*)-**3** (10)	7	90	96 (*S*)
17		(*S*)-**2** (20)	7	12	73 (*S*)
18		(*S*,*S*)-**3** (10)[e]	7	85	96 (*S*)
19		(*S*,*S*)-**3** (10)	24[f]	81	96 (*S*)
20		(*S*,*S*)-**3** (5)	9[g]	94	97 (*S*)
21	*p*-bromo-benzaldehyde	(*S*,*S*)-**3** (10)	15	85	98 (*S*)
22		(*S*)-**2** (20)	15	15	83 (*S*)
23	furfural	(*S*,*S*)-**3** (10)	18	96	97 (*S*)
24		(*S*)-**2** (20)	18	26	85 (*S*)

[a] Unless otherwise noted, the reaction of aldehyde and Bu_3SnCH_2-$CH{=}CH_2$ (1.1 equiv) was carried out in the presence of chiral bis-Ti^{IV} oxide (*S*,*S*)-**3** or chiral mono-Ti^{IV} (*S*)-**2** in CH_2Cl_2 at 0 °C with the given reaction time. [b] Unless specified, chiral bis-Ti^{IV} oxide (*S*,*S*)-**3** was prepared by Method A. [c] Determined by HPLC analysis with Chiralcel OD and OJ. [d] Determined by comparison of the sign of optical rotation with reported values. See [2l]. [e] Prepared by method B. [f] At −15 °C. [g] Use of two equivalents of allyltributyltin. [h] Determined by GC analysis on a chiral column (Chrompack CP-CHIRASIL-DEX CB). [i] Determined by GC analysis (Chrompack CP-CHIRASIL-DEX CB column) after conversion into its benzoate.

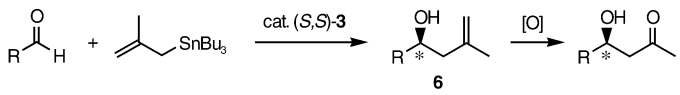
3) The enantioselectivity of this allylation is not sensitive to the reaction temperature (Table 1, entries 1 versus 3 and 16 versus 19).
4) The amount of chiral bis-Ti^{IV} oxide (*S*,*S*)-**3** can be reduced to 5 mol % without affecting the enantioselectivity (Table 1, entries 4, 5, 9, 10, and 20).

Application to natural products synthesis: Allylation products of aldehydes are useful intermediates for natural product syntheses.[1g] For example, Willis et al. recently reported the syntheses of tetrahydropyrans **9** and **10**,[15] starting from 3,4-diacetoxybenzaldehyde as shown in Scheme 6. These compounds, isolated from extracts of *Plectranthus sylvestris* (*Labiatae*), are potent in vitro antioxidants, inhibiting the Fe^{2+}-catalyzed autooxidation of linoleic acid, and also possess anti-inflammatory properties.[16] The crucial asymmetric allylation step was achieved by Brown's method.[17] This procedure required stoichiometric amount of chiral boron reagent (1.39 equiv (−)-DIPCl) and gave a less satisfactory result (76 % yield and 90 % *ee*). In contrast, treatment of 3,4-diacetoxybenzaldehyde with allyltributyltin (1.1 equiv) in the presence of catalytic (*S*,*S*)-**3** (10 mol %) at 0 °C for 16 h afforded the desired homoallylic alcohol **11** in 96 % yield and with 98 % *ee* (Scheme 6). Hence, our method was apparently far superior in terms of catalyst loading, chemical yield, and enantioselectivity.



Scheme 6. Synthesis of chiral tetrahydropyrans **9** and **10** through asymmetric allylation of 3,4-diacetoxyaldehyde with chiral bis-Ti^{IV} oxide (*S*,*S*)-**3**.

Catalytic asymmetric methallylation of aldehydes with chiral bis-Ti^{IV} oxides: We also utilized chiral bis-Ti^{IV} oxide (*S*,*S*)-**3** for the catalytic asymmetric methallylation of aldehydes.[8b] The enantioselective methallylation of prochiral aldehydes is an important asymmetric transformation in organic synthesis,[1] subsequent oxidative cleavage of the methallyl moiety providing optically active aldol products equivalent to those of an asymmetric crossed aldol reaction between aldehydes and the enolate of acetone (Scheme 7).



Scheme 7. Synthetic approach to chiral aldols through asymmetric methallylation of aldehydes with chiral bis-Ti^{IV} oxide (*S*,*S*)-**3**.

In contrast to the numerous examples of catalytic asymmetric allylation of prochiral aldehydes with allyltributyltin,[2] the corresponding asymmetric methallylation is rather difficult.[18] Indeed, compared to the allylic system, both reactivity and enantioselectivity in the catalytic asymmetric methallylation with ordinary chiral Lewis acid catalysts and methallyltributyltin were somewhat low, and did not exhibit broad applicability. In addition, such transformations required

 © 2003 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

longer reaction times at low temperatures. For example, catalytic asymmetric methallylation of cinnamaldehyde with BINOL-Ti^{IV} complex at $-20\,^{\circ}C$ for 12 h gave a 68% yield with 87% *ee*,[18a] while catalytic asymmetric methallylation of hydrocinnamaldehyde with BINAP-AgOTf complex at $-20\,^{\circ}C$ for 8 h afforded a 22% yield with 70% *ee*.[18f]

Treatment of hydrocinnamaldehyde **4** ($R = CH_2CH_2Ph$) with methallyltributyltin (1.1 equiv) under the influence of chiral bis-Ti^{IV} oxide (*S*,*S*)-**3** generated in situ (10 mol%) in CH_2Cl_2 at $0\,^{\circ}C$ for 30 min afforded 5-methyl-1-phenyl-5-hexen-3-ol **6** ($R = CH_2CH_2Ph$) in 63% yield with 94% *ee*. The absolute configuration of the homomethallylic alcohol was determined to be *R* by correlation with the authentic sample.[18a] It should be noted that both the reaction rate and the enantioselectivity of the methallylation are greatly lowered (e.g., 13% and 47% *ee* for hydrocinnamaldehyde) under similar reaction conditions with a chiral mono-Ti^{IV} catalyst (*S*)-**2** (20 mol%), derived from [Ti(O*i*Pr)$_4$] and (*S*)-BINOL by the literature procedure.[13]

Other selected examples are listed in Table 2. Several characteristic features of this methallylation follow:

Table 2. Asymmetric methallylation of aldehydes with methallyltributyltin catalyzed by chiral bis-Ti^{IV} oxide (*S*,*S*)-**3**.[a]

	Aldehyde	Ti catalyst [mol%]	Reaction time [h]	Yield [%]	*ee* [%][b] (config)[c]
1	$PhCH_2CH_2CHO$	(*S*,*S*)-**3** (10)	0.5	63	94 (*R*)
2		(*S*)-**2** (20)	0.5	13	47 (*R*)
3	PhCH=CHCHO	(*S*,*S*)-**3** (10)	2	90	94 (*S*)
4		(*S*)-**2** (20)	2	32	85 (*S*)
5	PhCHO	(*S*,*S*)-**3** (10)	0.5	94	95 (*S*)
6		(*S*)-**2** (20)	0.5	31	72 (*S*)
7	furfural	(*S*,*S*)-**3** (10)	2	88	91 (*S*)
8		(*S*)-**2** (20)	2	45	79 (*S*)
9	$CH_3(CH_2)_6CHO$	(*S*,*S*)-**3** (10)	20	87	92

[a] Unless otherwise noted, the reaction between aldehyde (0.33 M) and $Bu_3SnCH_2C(Me)=CH_2$ (1.1 equiv) was carried out in the presence of chiral bis-Ti^{IV} oxide (*S*,*S*)-**3** or chiral mono-Ti^{IV} (*S*)-**2** in CH_2Cl_2 at $0\,^{\circ}C$ for the given reaction time. [b] Determined by HPLC analysis on Chiralcel OD, OD-H and OB-H. [c] Determined by comparison of the sign of optical rotation with reported values. See ref. [18a].

1) The chiral bis-Ti^{IV} oxide (*S*,*S*)-**3** is applicable to various types of aldehydes and exhibits uniformly high asymmetric induction as well as high chemical yields.
2) The incorporation of the Ti–O–Ti unit in the chiral bis-Ti^{IV} catalyst (*S*,*S*)-**3** strongly accelerates the rate of methallylation of aldehyde carbonyls compared to the corresponding mono-Ti^{IV} catalyst (*S*)-**2**.
3) The absolute configuration of the homomethallylic alcohol **5** is predictable based on the use of either (*S*,*S*)-**3** or (*R*,*R*)-**3**.

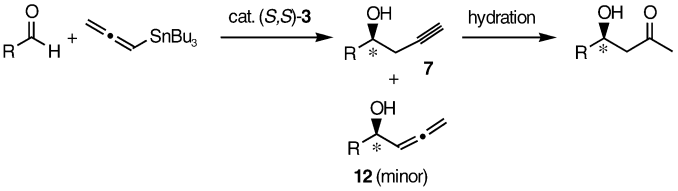
In the asymmetric methallylation of aldehydes with (*S*,*S*)-**3**, we found some effect of the concentration of the solvent. Selected results are summarized in Table 3, which clearly shows a high-dilution effect in correlation of the enantiopurity of methallylation products **6** ($R = CH_2CH_2Ph$, CH=CHPh).

Table 3. Dilution effect of aldehyde substrate on the asymmetric methallylation of aldehydes with methallyltributyltin catalyzed by chiral bis-Ti^{IV} oxide (*S*,*S*)-**3**.[a]

	Aldehyde	Concentration of substrate [M]	reaction condition [°C, h]	Yield [%]	*ee* [%][b] (config)
1	$PhCH_2CH_2CHO$	1.33	–20, 2	76	82 (*R*)
2		0.67	0, 2	76	93 (*R*)
3		0.33	0, 0.75	80	94 (*R*)
4		0.17	0, 2	73	94 (*R*)
5		0.083	0, 5	77	96 (*R*)
6	PhCH=CHCHO	0.33	0, 2	90	94 (*S*)
7		0.083	0, 11	90	96 (*S*)

[a] The reaction between aldehyde and $Bu_3SnCH_2C(Me)=CH_2$ (1.1 equiv) was carried out in the presence of chiral bis-Ti^{IV} oxide (*S*,*S*)-**3** (10 mol%) in CH_2Cl_2 under the given reaction conditions. [b] Determined by HPLC analysis on Chiralcel OD, OD-H, and OB-H.

Catalytic asymmetric propargylation of aldehydes with chiral bis-Ti^{IV} oxides: Catalytic asymmetric propargylation of prochiral aldehydes is also a valuable transformation, and the resulting homopropargylic alcohols are readily converted into the aldol products upon hydrolysis (Scheme 8). However, there have been few reports on catalytic asymmetric synthesis



Scheme 8. Synthetic approach to chiral aldols through asymmetric propargylation of aldehydes with chiral bis-Ti^{IV} oxide (*S*,*S*)-**3**.

of homopropargylic alcohols from prochiral aldehydes by use of allenyltributyltin,[19] presumably due to its low reactivity and regiochemical problems. An ordinary BINOL-Ti^{IV} complex for catalytic asymmetric propargylation required 50 or 100 mol% catalyst and very long reaction times (72 or 100 h).[19a] Recently, Yu et al. reported an improved method by the addition of a stoichiometric amount of Et_2BSiPr as a synergetic accelerator.[19b,c]

We also succeeded in carrying out asymmetric propargylation through the use of a catalytic amount of chiral bis-Ti^{IV} oxide (*S*,*S*)-**3**.[8b] With 10–20 mol% catalyst and longer reaction times, our method afforded the desired homopropargyl alcohol **7** in moderate yield and with high enantioselectivity, accompanied by a small amount of allenyl alcohol **12**, as indicated in Table 4.

Nonlinear effect with chiral bis-Ti^{IV} oxides: Nonlinear behavior in asymmetric catalysis is typically reported as product enantioselectivity (ee_{prod}) versus catalyst enantiomeric excess (ee_{cat}), where a positive deviation from the linear relationship is termed an *asymmetric amplification* of ee_{prod}.[20] Nonenantiopure chiral auxiliaries may be worthy of consideration in stoichiometric or catalytic enantioselective synthesis when they are associated with an asymmetric amplification.[21]

© 2003 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

Table 4. Asymmetric propargylation of aldehydes with allenyltributyltin catalyzed by chiral bis-Ti^{IV} oxide (*S*,*S*)-**3**.[a]

	Aldehyde	Ti catalyst (mol%)	Reaction time [h]	Yield [%] (ratio)[b]	*ee* [%][c] (config)[d]
1	$PhCH_2CH_2CHO$	(*S*,*S*)-**3** (10)	0, 18	50 (10:1)	92 (*R*)
2		(*S*,*S*)-**3** (10)[e]	0, 18 25, 6	64 (15:1)	92 (*R*)
3	PhCHO	(*S*,*S*)-**3** (10)	0, 18	28 (10:1)	95 (*S*)
4		(*S*,*S*)-**3** (20)[e]	0, 18 25, 6	69 (10:1)	92 (*S*)

[a] Unless otherwise noted, the reaction between aldehyde (0.33 M) and $Bu_3SnCH{=}C{=}CH_2$ (1.1 equiv) was carried out in the presence of chiral bis-Ti^{IV} oxide (*S*,*S*)-**3** in CH_2Cl_2 under the given reaction conditions. [b] Isomeric ratio of homopropargyl alcohol **7** and allenyl alcohol **12**. [c] Determined for major **7** by HPLC analysis on Chiralcel OD, OD-H, and AD-H. [d] Determined by comparison of the sign of optical rotation with reported values. See [19b]. [e] Use of excess $Bu_3SnCH{=}C{=}CH_2$ (3 equiv).

Table 5. Chiral Amplification in asymmetric allylation catalyzed by non-racemic bis-Ti^{IV} oxide **3**.[a]

ee [%] of **3**[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 between aldehyde **4** (R = CH_2CH_2Ph) (0.33 M) and allyltributyltin (1.1 equiv) was carried out in the presence of non-racemic bis-Ti^{IV} oxide **3** (10 mol%) in CH_2Cl_2 at 0 °C for 4 h. [b] In the non-racemic BINOL, (*S*)-BINOL was in excess. [c] See Experimental Section for methods C and D. [d] Determined by HPLC analysis on Chiralcel OD.

When we used partially resolved (*S*)-BINOL as chiral auxiliary for the preparation of non-racemic bis-Ti^{IV} oxide **3** (Method C), we observed a positive nonlinear effect in correlation of the enantiopurity of allylation product **5** (R = CH_2CH_2Ph) with the *ee* of (*S*)-BINOL, as shown in Table 5 and Figure 1. With such partially resolved (*S*)-BINOL, three kinds of bis-Ti^{IV} oxides exist: major (*S*,*S*)-**3**, minor (*S*,*R*)-**3**, and very minor (*R*,*R*)-**3** (Scheme 9). The big difference in the (*S*,*S*)-**3**/(*R*,*R*)-**3** catalyst ratio is assumed to be the reason for the positive nonlinear effect observed in these asymmetric allylation reactions. In marked contrast, however, optically pure bis-Ti^{IV} oxides (*S*,*S*)-**3** and (*R*,*R*)-**3** were prepared independently by starting from optically pure (*S*)- and (*R*)-BINOL, and asymmetric allylation by mixing them in a different ratio with the condition that (*S*,*S*)-**3** > (*R*,*R*)-**3** (Method D) gave rise to product **5** (R = CH_2CH_2Ph) in rather high yield without any chiral amplification (Table 5 and Figure 2). These results imply the following important points:

1) Symmetric (*S*,*S*)-**3** and (*R*,*R*)-**3** are more reactive than *meso*-(*S*,*R*)-**3** catalyst.
2) Bis-Ti^{IV} oxide **3** exists in solution as a monomeric species rather than as a dimeric one,[22]
3) Bis-Ti^{IV} oxide **3** is coordinatively stable, and no scrambling between (*S*,*S*)-**3** and (*R*,*R*)-**3** was observed under these allylation conditions.

Kinetic information may also help in the development of efficient synthetic strategies using non-enantiopure systems. Accordingly, we performed kinetic studies of these Ti^{IV} catalysts for the asymmetric allylation of hydrocinnamaldehyde. As expected, the catalytic activity of the homochiral (*S*,*S*)-**3** derived from optically pure (*S*)-BINOL is ca. 4 times greater than that of heterochiral (*S*,*R*)-**3** derived from *rac*-BINOL under the same reaction conditions (Figure 3).

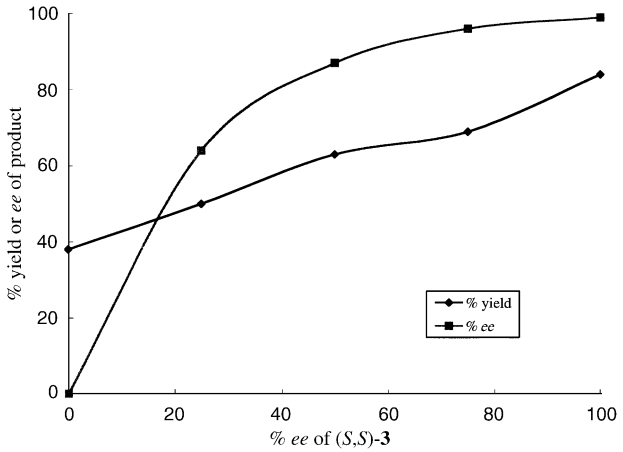
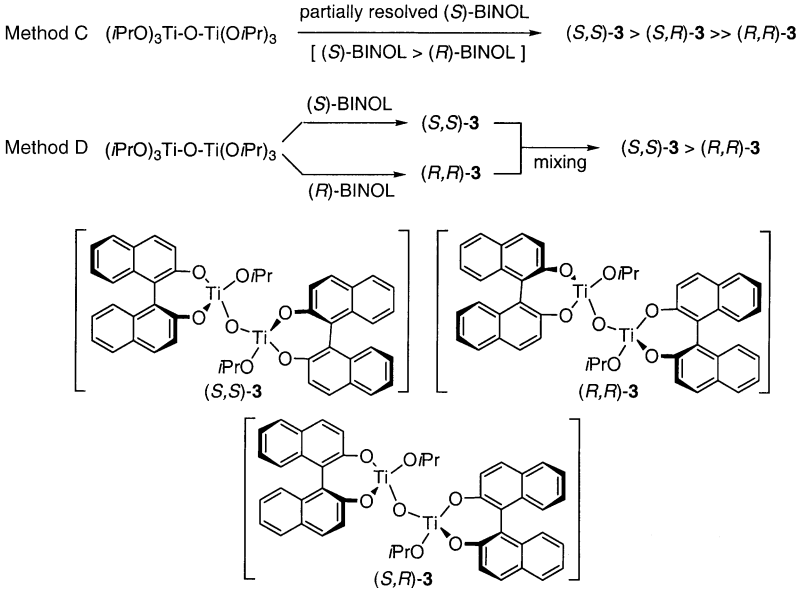


Figure 1. Reactivity and selectivity profile of chiral bis-Ti^{IV} oxide prepared by method C.



Scheme 9. Preparation of non-racemic bis-Ti^{IV} oxide (*S*,*S*)-**3** by methods C or D.

 © 2003 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

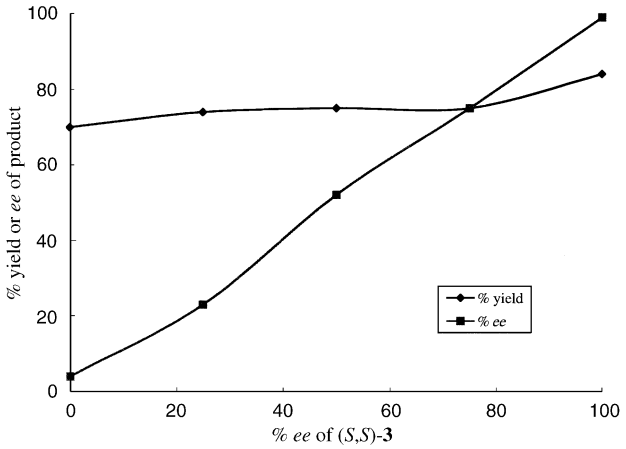


Figure 2. Reactivity and selectivity profile of chiral bis-Ti^{IV} oxide prepared by method D.

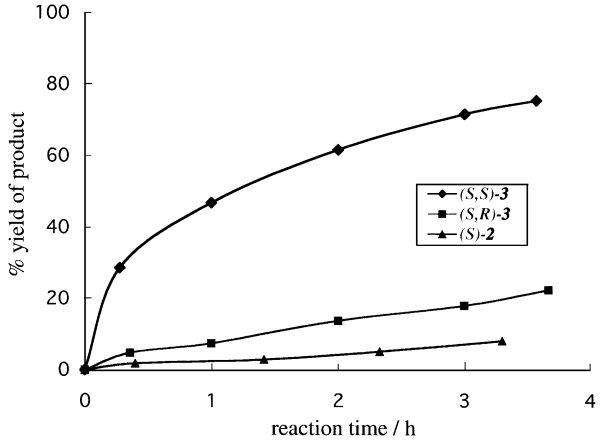
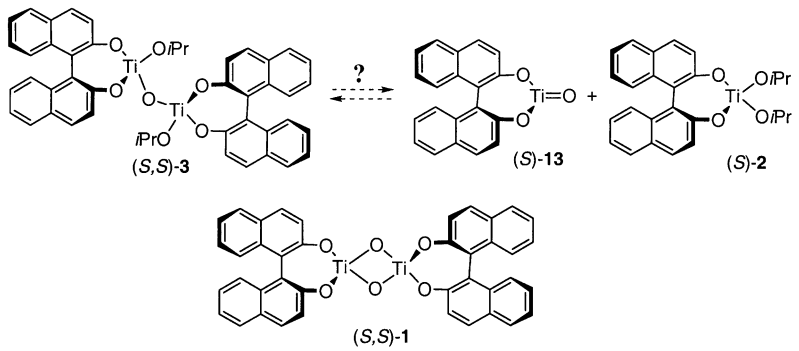


Figure 3. Catalytic activity of homochiral (*S*,*S*)-**3** vs. heterochiral (*S*,*R*)-**3**.

NMR study of carbonyl/Ti^{IV} Lewis acid complexes: The high reactivity of chiral Ti^{IV} complex (*S*,*S*)-**3** toward aldehyde carbonyls is attributed to the strong coordination of the mono-μ-oxo Ti–O–Ti structure to a carbonyl oxygen atom, thereby allowing strong activation of the aldehyde carbonyls. Such activation is also observed by ^{13}C NMR spectroscopy with 2,6-dimethyl-γ-pyrone as carbonyl substrate. Thus, 75 MHz ^{13}C NMR examination of the 1:1 2,6-dimethyl-γ-pyrone/mono-Ti^{IV} **2** complex in $CDCl_3$ at 20 °C showed that the original signal of the β-carbon atoms of the free pyrone at $\delta =$ 165.41 ppm shifted only slightly, to $\delta = 166.07$ ppm, suggesting feeble Lewis acidity of **2**. In contrast, the 1:1 2,6-dimethyl-γ-pyrone/(*S*,*S*)-**3** chelation complex under similar conditions shows a further downfield shift for the β-carbon atoms of the pyrone ($\delta = 167.90$ ppm). This result implies strong electrophilic activation of the pyrone carbonyl by (*S*,*S*)-**3**. Furthermore, addition of one more equivalent of 2,6-dimethyl-γ-pyrone to the 1:1 pyrone/(*S*,*S*)-**3** complex produced ^{13}C NMR chemical shifts at $\delta = 166.22$ ppm. Hence, two pyrone carbonyls coordinate separately to two Ti^{IV} centers of (*S*,*S*)-**3** in the 2:1 pyrone/(*S*,*S*)-**3** mixture.

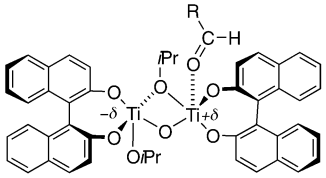
Elucidation of possible reaction pathways: Several possible reaction pathways to account for the activation phenomenon with chiral bis-Ti^{IV} oxide **3** have been considered. First, chiral bis-Ti^{IV} oxide (*S*,*S*)-**3** might exist as an equilibrium mixture of (*S*)-binaphthoxytitanium oxide (*S*)-**13**[23] and (*S*)-binaphthoxytitanium diisopropoxide (*S*)-**2**.[13] However, this possibility has been excluded by independent preparation of (*S*)-**13** and (*S*)-**2**, and subsequent carrying out of the asymmetric allylation of hydrocinnamaldehyde with allyltributyltin in the presence of a mixture of (*S*)-**13** and (*S*)-**2** (each 10 mol %) at 0 °C for 4 h to furnish homoallylic alcohol **5** (R = CH_2CH_2Ph) in 31 % yield and with 88 % *ee*. Since the use solely of (*S*)-**13** gave product **5** (R = CH_2CH_2Ph) in 20 % yield with 5 % *ee*, mixing of (*S*)-**13** and (*S*)-**2** seems partially to generate bis-Ti^{IV} oxide (*S*,*S*)-**3**. Indeed, on heating a mixture of (*S*)-**13** and (*S*)-**2** at reflux in CH_2Cl_2 for 3 h, we observed higher reactivity and selectivity (78 % yield with 94 % *ee*) in this allylation under similar conditions (Scheme 10).

It should be noted that (*S*)-binaphthoxytitanium μ-oxo complex (*S*,*S*)-**1** showed only low reactivity and selectivity under similar allylation condition (14 %, 25 % *ee*).[4] In addition, Keck's mono-Ti^{IV} reagent (20 mol %) derived from [Ti(O*i*Pr)$_4$] (20 mol %) and (*S*)-BINOL (40 mol %) was also examined for the asymmetric allylation of hydrocinnamaldehyde (53 % yield (93 % *ee*) at 0 °C for 4 h), again excluding the possibility of the generation of Keck's reagent by Methods A or B.[2d, 18b] Therefore, the high reactivity and selectivity of the chiral bis-Ti^{IV} oxide (*S*,*S*)-**3** might be attributable to the intramolecular coordination of one isopropoxy oxygen to the other titanium, thereby enhancing the otherwise weak Lewis acidity of the original titanium(IV) center for the carbonyl activation as shown in **14**. Alternatively, a carbonyl oxygen atom may coordinate simultaneously to two Ti centers as an intermediate or as a dynamic species, thereby producing strong activation of aldehyde carbonyls, such as depicted in **15**.[20, 24] In both cases, the mono-μ-oxo Ti–O–Ti bridge plays a key role in the activation of aldehyde carbonyl.

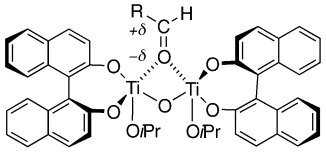


Scheme 10. Apparent partial generation of bis-Ti^{IV} oxide (*S*,*S*)-**3** by mixing of (*S*)-**13** and (*S*)-**2**.

© 2003 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim



14



15

Conclusion

In conclusion, a new chiral bis-Ti^{IV} complex (*S*,*S*)-**3** has been designed and can be utilized for the precise enantiofacial discrimination of aldehyde carbonyls for a new catalytic, practical, and enantioselective allylation of aldehydes with allyltributyltin and for similar reactions. This asymmetric approach provides a very useful way of obtaining high reactivity and selectivity by the simple incorporation of the M–O–M unit into the design of chiral Lewis acid catalysts.

Experimental Section

General: For thin layer chromatography (TLC) analysis, Merck precoated TLC plates (silica gel 60 GF_{254}, 0.25 mm) were used throughout this work. The products were purified by preparative column chromatography on silica gel 60 (Merck 1.09385.9025, 230–400 mesh). Infrared (IR) spectra were recorded on a Shimadzu FT-IR 8200A spectrometer. ^{1}H NMR spectra were measured on a JEOL JNM-FX400 (400 MHz) spectrometer. Chemical shifts of ^{1}H NMR spectra were reported relative to tetramethylsilane ($\delta = 0$ ppm). Splitting patterns were designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. ^{13}C NMR spectra were measured on a JEOL JNM-FX400 (100 MHz) spectrometer. Chemical shifts of ^{13}C NMR spectra were reported relative to $CDCl_3$ ($\delta = 77.0$). Analytical high performance liquid chromatography (HPLC) was performed on a Shimadzu LC-10A instrument with columns of Daicel Chiralcel OD, OJ, OD-H, OB-H, and AD-H ($\lambda = 210$ or 254 nm). Analytical gas–liquid phase chromatography (GC) was performed on a Shimadzu Model 14B instrument with a flame-ionization detector and a capillary column (Chrompack CP-Chirasil-Dex CB). Optical rotations were measured on a JASCO DIP-1000 digital polarimeter. Electrospray ionization mass spectra (ESI-MS) were recorded on an Applied Biosystems Mariner ESI-TOF Mass spectrometer.

All experimental work was carried out under an atmosphere of argon. CH_2Cl_2 was freshly distilled from calcium hydride. Toluene was freshly distilled from sodium metal. THF was freshly distilled from sodium benzophenone ketyl. Aldehydes were distilled under reduced pressure. Other simple chemicals were purchased and used as such.

Synthesis of chiral bis-Ti^{IV} oxide (*S*,*S*)-3 by Method A: Dried [Ti(O*i*Pr)$_4$] (88 μL, 0.3 mmol) was added under argon at 0 °C to a stirred solution of $TiCl_4$ (0.1 mmol) in CH_2Cl_2 (2 mL). The solution was allowed to warm to room temperature. After 1 h, silver(I) oxide (46.4 mg, 0.2 mmol) was added at room temperature, and the whole mixture was stirred for 5 h with exclusion of direct light. The mixture was diluted with CH_2Cl_2 (4 mL), and treated with (*S*)-BINOL (114.5 mg, 0.4 mmol) at room temperature for 2 h to furnish chiral bis-Ti^{IV} oxide (*S*,*S*)-**3** in CH_2Cl_2 solvent.

Synthesis of chiral bis-Ti^{IV} oxide (*S*,*S*)-3 by method B: Dried [Ti(O*i*Pr)$_4$] (88 μL, 0.3 mmol) was added under argon at 0 °C to a stirred solution of $TiCl_4$ (0.1 mmol) in CH_2Cl_2 (2 mL). The solution was allowed to warm to room temperature. After 1 h, (*S*)-BINOL (114.5 mg, 0.4 mmol) was added at room temperature, and the solution was stirred for 2 h. The mixture was cooled to 0 °C, and treated at 0 °C with silver(I) oxide (46.4 mg, 0.2 mmol). The mixture was allowed to warm to room temperature, and stirred for 5 h with exclusion of direct light to furnish chiral bis-Ti^{IV} oxide (*S*,*S*)-**3**, which was diluted with CH_2Cl_2 (4 mL) before use.

((*S*)-Binaphthoxy)Ti(O*i*Pr)$_2$ (*S*)-2: Dried [Ti(O*i*Pr)$_4$] (886 μL, 3 mmol) was added at room temperature to a suspension of dried (*S*)-BINOL (858 mg, 3 mmol) in CH_2Cl_2 (25 mL). After stirring for 1 h at that temperature, the reaction mixture was azeotroped until the volume of the solution had been reduced to 10 mL. Further concentration was continued under reduced pressure. The resulting orange residue was dissolved in diethyl ether (20 mL) and allowed to stand for several hours at 0 °C. The resulting needle-crystalline material was decanted and the supernatant solution was removed by syringe. The ether solvent was removed under reduced pressure to give ((*S*)-binaphthoxy)Ti(O*i*Pr)$_2$ (*S*)-**2** (2.0 g, 4.3 mmol, 72 %) as yellowish orange crystals: ^{1}H NMR (CD_2Cl_2): $\delta = 7.93$ (d, $J = 8.1$ Hz, 2H; Ar–H), 7.54 (d, $J = 8.7$ Hz, 2H; Ar–H), 7.40 (ddd, $J = 3.1$, 4.9, 8.1 Hz, 2H; Ar–H), 7.14–7.24 (m, 4H; Ar–H), 6.79 (d, $J = 8.7$ Hz, 2H; Ar–H), 4.55 (sept, $J = 6.0$ Hz, 2H; O–CH), 1.15 (d, $J = 6.0$ Hz, 6H; CH_3), 1.09 (d, $J = 6.0$ Hz, 6H; CH_3) ppm; ^{13}C NMR (CD_2Cl_2): $\delta = 158.75$, 132.80, 129.88, 128.90, 127.96, 126.35, 125.27, 123.17, 120.96, 118.57, 80.84, 25.02, 24.79 ppm.

ESI-MS analysis of chiral bis-Ti^{IV} oxide (*S*,*S*)-3: [Ti(O*i*Pr)$_4$] (88 mL, 0.3 mmol) was added under argon at 0 °C to a stirred solution of $TiCl_4$ (0.1 mmol) in CH_2Cl_2 (2 mL), and the mixture was then allowed to warm to room temperature. After 1 h, Ag_2O (46.4 mg, 0.2 mmol) was added at room temperature, and the mixture was stirred for 5 h with exclusion of direct light. The mixture was diluted with CH_2Cl_2 (4 mL), and treated at room temperature with (*S*)-BINOL (114.5 mg, 0.4 mmol) for 2 h to furnish chiral bis-Ti^{IV} oxide (*S*,*S*)-**3** in CH_2Cl_2. This mixture was filtered to remove AgCl, and THF (2 mL) was then added to the resulting CH_2Cl_2 solution at room temperature. An electrospray ionization mass spectrum (ESI-MS) was recorded on an Applied Biosystems Mariner ESI-TOF mass spectrometer. Experimental conditions were as follows: direct infusion by syringe pump; sample concentration, 50 μM in CH_3CN; flow rate, 5 μL min^{-1}; nebulizing gas, N_2; spray tip voltage, 3.5 kV; API interface nozzle potential, 80 V; API interface quad RF voltage, 300 V; API interface nozzle temperature, 80 °C; found: 943 $[M+2\,THF+H]^+$; $[C_{54}H_{55}O_9Ti_2]^+$ calcd 943.

Synthesis of [$Ti_2(\mu$-O)$Cl_2(\eta^2$-guaiacolato)$_4$] (8) with Ag_2O: 2-Methoxyphenol (660 μL, 6 mmol) was added under argon at room temperature to a stirred solution of $TiCl_4$ (329 μL, 3 mmol) in toluene (20 mL). After 24 h, the solution was concentrated to about 12 mL, and the reddish-brown precipitate was filtered off, washed with toluene, and dried under vacuum. Recrystallization from toluene afforded *cis*-[$TiCl_2(\eta^2$-guaiacolato)$_2$];[13] ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.39–7.26$ (m, 5H; Ph–H), 5.89–5.75 (m, 1H; C–CH=C), 5.22–5.13 (m, 2H; C=CH_2), 4.77–4.72 (m, 1H; O–CH), 2.60–2.45 (m, 2H; CH_2–C=C), 2.02 ppm (d, $J = 3.3$ Hz, 1H; OH).

Ag_2O (46.4 mg, 0.2 mmol) was added at room temperature to a stirred solution of *cis*-[$TiCl_2(\eta^2$-guaiacolato)$_2$] (146.0 mg, 0.4 mmol) in freshly distilled CH_2Cl_2 (5 mL), and the mixture was stirred for 5 h with exclusion of direct light. After removal of AgCl by filtration, the red solution was concentrated under vacuum. The residue was dissolved in $CDCl_3$. The solution was then transferred by cannula to a NMR tube, which was capped with a rubber septum and filled with argon. The ^{1}H NMR spectrum was recorded at room temperature, and was spectroscopically identical with that of [$Ti_2(\mu$-O)$Cl_2(\eta^2$-guaiacolato)$_4$] (**8**) prepared by the reported procedure by use of H_2O;[13] ^{1}H NMR (400 MHz, C_6D_6): $\delta = 6.84$ (m, 4H; 4 × 4-HAr), 6.61 (m, 8H; 4 × 3,6-HAr), 6.14 (m, 4H; 4 × 5-HAr), 3.42 ppm (s, 12H; 4 × OCH_3).

Representative procedure for asymmetric allylation of aldehydes (by method A): Compound (*S*,*S*)-**3** (0.2 mmol) [prepared by Method A], generated in situ in CH_2Cl_2 (6 mL), was cooled to −15 °C, and treated sequentially at −15 °C with hydrocinnamaldehyde (263 μL, 2.0 mmol) and allyltributyltin (682 μL, 2.2 mmol). The mixture was allowed to warm to 0 °C and stirred for 4 h. The reaction mixture was quenched with saturated $NaHCO_3$, and extracted with ether. The organic extracts were dried over Na_2SO_4. Evaporation of solvents and purification of the residue by column chromatography on silica gel (ether/hexane 1:4 as eluent) gave (*R*)-1-phenyl-5-hexen-3-ol **5** (R = CH_2CH_2Ph) as a colorless oil (296.1 mg, 84 % yield): ^{1}H NMR ($CDCl_3$): $\delta = 7.32–7.17$ (m, 5H; Ar–H) , 5.81 (m, 1H; C–CH=C), 5.14 (dd, $J = 1.2$, 13.2 Hz, 2H; C=CH_2), 3.68 (m, 1H; O–CH), 2.81 (m, 1H; $PhCH_2$), 2.69 (m, 1H; $PhCH_2$), 2.32 (m, 1H; CH_2–C=C), 2.18 (m, 1H; CH_2–C=C), 1.80 (m, 2H; Ph–C–CH_2), 1.61 (d, $J = 4.4$ Hz, 1H; OH) ppm. The absolute configuration and enantiomeric purity of the product were determined as *R* and 99 % *ee* by analytical HPLC analysis [Daicel Chiralcel OD, *i*PrOH/hexane 1:20, flow rate = 0.5 mL min^{-1}, t_R = 18.86 min (*S* isomer), $t_R = 29.17$ min (*R* isomer)] by comparison with the racemic and authentic samples.

 © 2003 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

Asymmetric allylation of 3,4-diacetoxybenzaldehyde: A solution of chiral bis-Ti^{IV} oxide (*S*,*S*)-**3** (prepared by Method A) was cooled to $-15\,^{\circ}C$, and treated sequentially at $-15\,^{\circ}C$ with 3,4-diacetoxybenzaldehyde (2 mmol) and allyltributyltin (682 μL, 2.2 mmol). The mixture was allowed to warm to $0\,^{\circ}C$ and stirred for 16 h. The reaction mixture was quenched with saturated $NaHCO_3$, and extracted with ether. The organic extracts were dried over Na_2SO_4. Evaporation of solvents and purification of the residue by column chromatography on silica gel (EtOAc/hexane 1:3) gave (*S*)-1-(3,4-diacetoxyphenyl)-3-buten-1-ol **5** (R = 3,4-diacetoxyphenyl)[15] as a colorless oil (499.6 mg, 95% yield): $[\alpha]_D^{22} = -35.5$ ($c = 1.25$ in $CHCl_3$); ^1H NMR ($CDCl_3$): $\delta = 7.26-7.15$ (m, 3H; Ar−H), 5.81 (m, 1H; C*H*=CH_2), 5.19 (m, 1H; C=CH_2), 5.15 (m, 1H; C=CH_2), 4.74 (m, 1H; O−CH), 2.48 (m, 2H; CH_2−C=C), 2.29 (d, $J = 1.2$ Hz, 6H; $2 \times CH_3$), 2.11 (d, $J = 3.2$ Hz, 1H; OH) ppm.

The absolute configuration and enantiomeric purity of the product were determined as *S* and 98% *ee* by HPLC analysis (Daicel Chiralcel OD-H, hexane/*i*PrOH 4:1, flow rate = 0.5 mL min^{-1}, $\lambda = 210$ nm), $t_R = 16.13$ min (*S* isomer), $t_R = 17.73$ min (*R* isomer) in comparison with the authentic sample.

Representative procedure for asymmetric methallylation of aldehydes: Compound (*S*,*S*)-**3** (0.2 mmol) [prepared by Method A], generated in situ in CH_2Cl_2 (6 mL), was cooled to $-15\,^{\circ}C$, and treated sequentially at $-15\,^{\circ}C$ with hydrocinnamaldehyde (263 μL, 2.0 mmol) and methallyltributyltin (759.3 mg, 2.2 mmol). The mixture was allowed to warm to $0\,^{\circ}C$ and was stirred for 30 min. The reaction mixture was quenched with saturated $NaHCO_3$, and extracted with ether. The organic extracts were dried over Na_2SO_4. Evaporation of solvents and purification of the residue by column chromatography on silica gel (EtOAc/hexane 1:12 as eluent) gave (*R*)-5-methyl-1-phenyl-5-hexen-3-ol **6** (R = CH_2CH_2Ph) as a colorless oil (239.2 mg, 63% yield): ^1H NMR ($CDCl_3$): $\delta = 7.31-7.20$ (m, 5H; Ar−H), 4.89 (s, 1H; C=CH_2), 4.80 (s, 1H; C=CH_2), 3.75 (m, 1H; O−CH), 2.82 (m, 1H; $PhCH_2$), 2.71 (m, 1H; $PhCH_2$), 2.15 (m, 2H; CH_2−CMe=C), 1.81 (m, 2H; Ph−C−CH_2), 1.74 (s, 3H; CH_3), 1.72 (d, $J = 2.8$ Hz, 1H; OH) ppm. The absolute configuration and enantiomeric purity of the product were determined as *R* and 94% *ee* by analytical HPLC analysis [Daicel Chiralcel OD-H, *i*PrOH/hexane 1:30; flow rate = 0.5 mL min^{-1}, $\lambda =$ 254 nm), $t_R = 19.07$ min (*S* isomer), $t_R = 29.46$ min (*R* isomer)] by comparison with the racemic and authentic samples.

Representative procedure for asymmetric propargylation of aldehydes: Compound (*S*,*S*)-**3** (0.2 mmol) [prepared by Method A], generated in situ in CH_2Cl_2 (6 mL), was cooled to $-15\,^{\circ}C$, and treated sequentially at $-15\,^{\circ}C$ with hydrocinnamaldehyde (263 μL, 2.0 mmol) and allenyltributyltin (724 mg, 2.2 mmol). The mixture was allowed to warm to $0\,^{\circ}C$ and was stirred for 18 h. The reaction mixture was quenched with saturated $NaHCO_3$, and extracted with ether. The organic extracts were dried over Na_2SO_4. Evaporation of solvents and purification of the residue by column chromatography on silica gel (EtOAc/hexane 1:10 as eluent) gave (*R*)-1-phenyl-5-hexyn-3-ol **7** (R = CH_2CH_2Ph) as a colorless oil (158.7 mg, 45.5% yield) accompanied by (*R*)-1-phenyl-4,5-hexadien-3-ol **12** (R = CH_2CH_2Ph) (15.6 mg, 4.5% yield). The absolute configuration and enantiomeric purity of the major product **7** (R = CH_2CH_2Ph) were determined as *R* and 92% *ee* by analytical HPLC analysis [Daicel Chiralcel OD-H, *i*PrOH/hexane 1:30, flow rate = 0.5 mL min^{-1}, $t_R =$ 26.42 min (*S* isomer), $t_R = 42.71$ min (*R* isomer)] by comparison with the racemic and authentic samples.

(*R*)-1-Phenyl-5-hexyn-3-ol: ^1H NMR ($CDCl_3$): $\delta = 7.31-7.19$ (m, 5H; Ar−H), 3.78 (m, 1H; O−CH), 2.80 (m, 1H; $PhCH_2$), 2.70 (m, 1H; $PhCH_2$), 2.40 (m, 2H; CH_2CCH), 2.06 (t, $J = 2.4$ Hz, 1H; CH_2CC*H*), 1.95 (br s, 1H; OH), 1.88 (m, 2H; $PhCH_2CH_2$) ppm.

(*R*)-1-Phenyl-4,5-hexadien-3-ol: ^1H NMR ($CDCl_3$): $\delta = 7.31-7.17$ (m, 5H; Ar−H), 5.26 (dd, $J = 6.0$, 12.8 Hz, 1H; C*H*CCH_2), 4.88 (dt, $J = 2.4$, 6.0 Hz, 2H; CHCCH_2), 4.26 (m, 1H; O−CH), 2.77–2.55 (m, 2H; $PhCH_2$), 1.97 (m, 2H; $PhCH_2CH_2$), 1.84 (br s, 1H; OH) ppm.

Linear versus positive nonlinear effects: **preparation of catalyst solution by method C**: The catalyst solution (*x*% *ee*) for 2 mmol scale reaction was prepared by Method A by the use of partially resolved (*S*)-BINOL, which was prepared by mixing (*S*)-BINOL (*y* mmol) and *rac*-BINOL (2 mmol, $y + z = 0.4$, $x = 250y$).

Preparation of catalyst solution by method D: The catalyst solution (*x*% *ee*) for a 2 mmol scale reaction was prepared as follows; optically pure (*S*,*S*)-**3** and (*R*,*R*)-**3** solutions were prepared independently by Method A, and they were mixed in different ratios [(*S*,*S*)-**3** (*y* mmol) and (*R*,*R*)-**3** (*z* mmol), $y + z = 0.4$, $\times = 250(y - z)$] before the asymmetric allylation.

General procedure for kinetic studies: A solution of chiral Ti^{VI} catalyst (prepared in $CDCl_3$ by Method A, 0.1 or 0.2 mmol) was cooled to $-15\,^{\circ}C$, and was treated sequentially at $-15\,^{\circ}C$ with aldehyde (1 mmol) and allyltributyltin (341 μL, 1.1 mmol). The resulting solution was transferred by cannula to a NMR tube capped with a rubber septum, placed under argon, and cooled to $0\,^{\circ}C$, and the ^1H NMR spectrum was recorded at $0\,^{\circ}C$.

General procedure for NMR studies on the 1:1 Lewis acid – carbonyl complexes: 2,6-Dimethyl-γ-pyrone (47.2 mg, 0.38 mmol) was added at room temperature under argon to a solution of (*S*,*S*)-**3** (0.4 mmol, prepared by Method A) in degassed $CDCl_3$ (1.5 mL). After being stirred for 0.5 h at that temperature, the resultant solution was transferred by cannula to a NMR tube, which was capped with a rubber septum and filled with argon. The ^1H and ^{13}C NMR were recorded at room temperature.

Synthesis of chiral (Binaphthoxy)Ti=O (*S*)-13:[23] A solution of H_2O (36 μL, 2 mmol) in isopropanol (0.8 mL) was added at $0\,^{\circ}C$ under argon to a stirred solution of Ti(O*i*Pr)$_4$ (590 μL, 2 mmol) in isopropanol (2 mL). The mixture was then allowed to warm to room temperature. It was then concentrated under reduced pressure, and the (*i*PrO)$_2$Ti=O residue was diluted with CH_2Cl_2 (as a 0.5 M solution). A CH_2Cl_2 solution of (*i*PrO)$_2$Ti=O (0.5 M, 1.6 mL, 0.8 mmol) was added under argon at room temperature to a stirred solution of (*S*)-BINOL (229.1 mg, 0.8 mmol) in toluene (4 mL). The mixture was stirred at room temperature for 1 h and was then heated at reflux for azeotropic removal of isopropanol, followed by complete removal of toluene under reduced pressure to furnish [(*S*)-binaphthoxy]Ti=O (*S*)-**13**.

Asymmetric allylation with ((*S*)-binaphthoxy)Ti=O (*S*)-13 and (*S*)-binaphthoxytitanium diisopropoxide (*S*)-2: ((*S*)-Binaphthoxy)Ti=O (*S*)-**13**[23] and (*S*)-binaphthoxytitanium diisopropoxide (*S*)-**2**[14] were prepared independently as described above, and asymmetric allylation of hydrocinnamaldehyde with allyltributyltin by mixing of (*S*)-**13** and (*S*)-**2** (each 10 mol%) at $0\,^{\circ}C$ for 4 h then afforded homoallylic alcohol **5** (R = CH_2CH_2Ph) in 31% yield and with 88% *ee*. Since the use solely of **3** gave product **5** (R = CH_2CH_2Ph) in 20% yield with 5% *ee*, the mixing of (*S*)-**13** and (*S*)-**2** seems partially to generate bis-Ti^{IV} oxide (*S*,*S*)-**3**. Indeed, on heating a mixture of (*S*)-**13** and (*S*)-**2** at reflux in CH_2Cl_2 for 3 h, we observed higher reactivity and selectivity (78% yield with 94% *ee*) in this allylation under similar conditions.

Synthesis of chiral bis-μ-oxo Ti(IV) catalyst (*S*,*S*)-1:[4] [Ti(O*i*Pr)$_4$] (118 mL, 0.4 mmol) and then H_2O (7.2 mL, 0.4 mmol) were added under argon at room temperature to a stirred solution of (*S*)-BINOL (114.5 mg, 0.4 mmol) in toluene (4 mL). The mixture was heated at reflux for 2 h. Azeotropic removal of 2-propanol followed by complete removal of toluene under reduced pressure afforded chiral bis μ-oxo Ti^{IV} catalyst (*S*,*S*)-**1**.

Asymmetric allylation with chiral bis-μ-oxo Ti^{IV} catalyst (*S*,*S*)-1: Asymmetric allylation of hydrocinnamaldehyde with allyltributyltin in the presence of (*S*)-binaphthoxytitanium μ-oxo complex (*S*,*S*)-**1** at $0\,^{\circ}C$ for 4 h afforded homoallylic alcohol **5** (R = CH_2CH_2Ph) in 14% yield and with 25% *ee*.[4]

Asymmetric allylation with modified Keck's reagent. Keck's mono-Ti^{IV} reagent (20 mol%), derived from [Ti(O*i*Pr)$_4$] (20 mol%) and (*S*)-BINOL (40 mol%), was utilized for the asymmetric allylation of hydrocinnamaldehyde with allyltributyltin at $0\,^{\circ}C$ for 4 h to furnish homoallylic alcohol **5** (R = CH_2CH_2Ph) in 53% yield and with 93% *ee*.[2d]

Acknowledgements

This work was supported by a Grant-in-Aid for Scientific Research (No. 13853003) from the Ministry of Education, Culture, Sports, Science and Technology, Japan. H. H. thanks the Japan Society for the Promotion of Science for Young Scientists for Research Fellowships.

[1] Reviews: a) R. Noyori, *Asymmetric Catalysis in Organic Synthesis*, John Wiley and Sons, New York, **1993**; b) K. Maruoka, H. Yamamoto in *Catalytic Asymmetric Synthesis* (Ed.: I. Ojima), VCH, New York, **1993**, p 413; c) K. Mikami, *Advances in Catalytic Process* (Ed.: M. P.

© 2003 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

Doyle), JAI Press, Greenwich, **1995**; d) A. H. Hoveyda, J. P. Morken, *Angew. Chem.* **1996**, *108*, 1378; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1262; e) A. Yanagisawa in *Comprehensive Asymmetric Catalysis* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **1999**, p 965; f) S. E. Denmark, N. G. Almstead in *Modern Carbonyl Chemistry* (Ed.: J. Otera), VCH, Weinheim, **2000**, p 299; g) S. R. Chemler, W. R. Roush in *Modern Carbonyl Chemistry* (Ed.: J. Otera), VCH, Weinheim, **2000**, p 403.

[2] a) S. Aoki, K. Mikami, M. Terada, T. Nakai, *Tetrahedron* **1993**, *49*, 1783; b) A. L. Costa, M. G. Piazza, E. Tagliavini, C. Trombini, A. Umani-Ronchi, *J. Am. Chem. Soc.* **1993**, *115*, 7001; c) G. E. Keck, K. H. Tarbet, L. S. Geraci, *J. Am. Chem. Soc.* **1993**, *115*, 8467; d) G. E. Keck, L. S. Geraci, *Tetrahedron Lett.* **1993**, *34*, 7827; e) J. W. Faller, D. W. Sams, X. Liu, *J. Am. Chem. Soc.* **1996**, *118*, 1217; f) D. R. Gauthier Jr., E. M. Carreira, *Angew. Chem.* **1996**, *108*, 2521; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2363; g) C.-M. Yu, H.-S. Choi, W.-H. Jung, S.-S. Lee, *Tetrahedron Lett.* **1996**, *37*, 7095; h) C.-M. Yu, H.-S. Choi, W.-H. Jung, H.-J. Kim, J. Shin, *Chem. Commun.* **1997**, 761; i) C.-M. Yu, H.-S. Choi, S.-K. Yoon, W.-H. Jung, *Synlett* **1997**, 889; j) J. A. Marshall, *Chemtracts* **1997**, *10*, 649; k) E. Brenna, L. Scaramelli, S. Serra, *Synlett* **2000**, 357; l) S. Kii, K. Maruoka, *Tetrahedron Lett.* **2001**, *42*, 1935; m) H. Hanawa,S. Kii, K. Maruoka, *Adv. Synth. Catal.* **2001**, *343*, 57; n) K. Maruoka, *Pure Appl. Chem.* **2002**, *74*, 123; o) S. Kii, K. Maruoka, *Chirality* **2003**, *15*, 68.

[3] a) T. J. Boyle, D. L. Barnes, J. A. Happert, L. Morales, F. Takusagawa, *Organometallics* **1992**, *11*, 1112; b) N. W. Eilerts, J. A. Heppert, M. L. Kennedy, F. Takusagawa, *Inorg. Chem.* **1994**, *33*, 4813; c) T. J. Boyle, N. W. Eilerts, J. A. Happert, F. Takusagawa, *Organometallics* **1994**, *13*, 2218; d) T. J. Davis, J. Balsells, P. Carroll, P. J. Walsh, *Org. Lett.* **2001**, *3*, 699; e) J. Balsells, T. J. Davis, P. Carroll, P. J. Walsh, *J. Am. Chem. Soc.* **2002**, *124*, 10336.

[4] a) M. Terada, K. Mikami, *J. Chem. Soc. Chem. Commun.* **1994**, 833. b) D. Kitamoto, H. Imma, T. Nakai, *Tetrahedron Lett.* **1995**, *36*, 1861.

[5] a) M. Terada, Y. Matsumoto, Y. Nakamura, K. Mikami, *Inorg. Chim. Acta* **1999**, *296*, 267; b) M. Breuning, E. J. Corey, *Org. Lett.* **2001**, *3*, 1559.

[6] D. Kitamoto, H. Imma, T. Nakai, *Tetrahedron Lett.* **1995**, *36*, 1861.

[7] a) H. Hanawa, N. Abe, K. Maruoka, *Tetrahedron Lett.* **1999**, *40*, 5365; b) N. Abe, H. Hanawa, K. Maruoka, M. Sasaki, M. Miyashita, *Tetrahedron Lett.* **1999**, *40*, 5369.

[8] a) H. Hanawa, T. Hashimoto, K. Maruoka, *J. Am. Chem. Soc.* **2003**, *125*, 1708. b) S. Konishi, H. Hanawa, K. Maruoka, *Tetrahedron: Asymmetry*, in press.

[9] a) M. M. Olmstead, P. P. Power, M. Viggiano, *J. Am. Chem. Soc.* **1983**, *105*, 2927; b) L. M. Alvaro, T. Cuenca, J. C. Flores, P. Royo, M. A. Pellinghelli, A. Tiripicchio, *Organometallics* **1992**, *11*, 3301; c) F. Franceschi, E. Gallo, E. Solari, C. Floriani, A. Chiesi-Villa, C. Rizzoli, N. Re, A. Sgamellotti, *Chem. Eur. J.* **1996**, *2*, 1466; d) N. Kuhn, T. Kratz, D. Bläser, R. Boese, *Inorg. Chim. Acta* **1995**, *238*, 179; e) A. Kayal, A. F. Ducruet, S. C. Lee, *Inorg. Chem.* **2000**, *39*, 3696; f) M. L. N. Rao, H. Houjou, K. Hiratani, *Chem. Commun.* **2002**, 420.

[10] M. P. McDaniel, *U.S. Pat.* 4402864, **1983**.

[11] ((*S*)-Binaphthoxy)isopropoxytitanium chloride:D. Seebach, A. K. Beck, S. Roggo, A. Wonnacott, *Chem. Ber.* **1985**, *118*, 3673.

[12] M. Bonchio, G. Licini, G. Modena, O. Bortolini, S. Moro, W. A. Nugent, *J. Am. Chem. Soc.* **1999**, *121*, 6258.

[13] P. Sobota, K. Przybylak, J. Utko, L. B. Jerzykiewicz, A. J. L. Pombeiro, M. F. C. Guedes da Silva, K. Szczegot, *Chem. Eur. J.* **2001**, *7*, 951.

[14] a) Private communication from Prof. K. B. Sharpless: C. A. Martin, Ph.D. thesis, MIT, **1988**; b) J. T. Wang, X. Fan, X. Feng, Y. M. Qian, *Synthesis* **1989**, 291; c) K. Mikami in *Encyclopedia of Reagents for Organic Synthesis*, *Vol. 1* (Ed.: L. A. Paquette), Wiley, Chichester, **1995**, p 407.

[15] S. R. Crosby, J. R. Harding, C. D. King, G. D. Parker, C. L. Willis, *Org. Lett.* **2002**, *4*, 3407.

[16] M. Juch, P. Rüedi, *Helv. Chim. Acta* **1997**, *80*, 436.

[17] H. C. Brown, K. S. Bhat, R. S. Randad, *J. Org. Chem.* **1987**, *52*, 319.

[18] a) G. E. Keck, D. Krishnamurthy, M. C. Grier, *J. Org. Chem.* **1993**, *58*, 6543; b) S. Weigand, R. Brückner, *Chem. Eur. J.* **1996**, *2*, 1077; c) G. E. Keck, T. Yu, *Org. Lett.* **1999**, *1*, 289; d) G. E. Keck, J. A. Covel, T. Schiff, T. Yu, *Org. Lett.* **2002**, *4*, 1189; e) C.-M. Yu, J.-Y. Lee, B. So, J. Hong, *Angew. Chem.* **2002**, *114*, 169; *Angew. Chem. Int. Ed.* **2002**, *41*, 161; f) A. Yanagisawa, A. Ishiba, H. Nakashima, H. Yamamoto, *Synlett* **1997**, 88; g) M. Inoue, T. Suzuki, M. Nakada, *J. Am. Chem. Soc.* **2003**, *125*, 1140.

[19] a) G. E. Keck, D. Krishnamurthy, X. Chen, *Tetrahedron Lett.* **1994**, *35*, 8323; b) C.-M. Yu, S.-K. Yoon, H.-S. Choi, K. Baek, *Chem. Commun.* **1997**, 763; c) C.-M. Yu, S.-K. Yoon, K. Baek, J.-Y. Lee, *Angew. Chem.* **1998**, *110*, 2504; *Angew. Chem. Int. Ed.* **1998**, *37*, 2392. See also: M. Bandini, P. G. Cozzi, P. Melchiorre, R. Tino, A. Umani-Ronchi, *Tetrahedron: Asymmetry* **2001**, *12*, 1063.

[20] a) C. Girard, H. B. Kagan, *Angew. Chem.* **1998**, *110*, 3088; *Angew. Chem. Int. Ed.* **1998**, *37*, 2922; b) H. B. Kagan, T. O. Luukas in *Comprehensive Asymmetric Catalysis* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **1999**, p 101; c) K. Soai, I. Shibata in *Catalytic Asymmetric Synthesis* (Ed.: I. Ojima), Wiley-VCH, New York, **2000**, p 413; d) K. Mikami, M. Terada, T. Korenaga, Y. Matsumoto, M. Ueki, R. Angelaud, *Angew. Chem.* **2000**, *112*, 3676; *Angew. Chem. Int. Ed.* **2000**, *39*, 3532; e) D. G. Blackmond, *Acc. Chem. Res.* **2000**, *33*, 402; f) H. B. Kagan, *Adv. Synth. Catal.* **2001**, *343*, 227.

[21] K. Mikami, M. Terada, T. Korenaga, Y. Matsumoto, S. Matsukawa, *Acc. Chem. Res.* **2000**, *33*, 391.

[22] Some chiral BINOL-Ti^{IV} complexes exist as dimeric species that exhibit chiral amplification phenomena. See[2b].

[23] a) B. C. Bradley, R. Gaze, W. Wardlaw, *J. Chem. Soc.* **1955**, 721; b) T. Mukaiyama, A. Inubushi, S. Suda, R. Hara, S. Kobayashi, *Chem. Lett.* **1990**, 1015.

[24] a) N. Asao, S. Kii, H. Hanawa, K. Maruoka, *Tetrahedron Lett.* **1998**, *39*, 3729; b) S. Kii, T. Hashimoto, K. Maruoka, *Synlett* **2002**, 931; c) N. Morohashi, T. Hattori, K. Yokomakura, C. Kabuto, S. Miyano, *Tetrahedron Lett.* **2002**, *43*, 7769.

Received: April 28, 2003 [F5078]

 © 2003 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim