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Catalytic asymmetric methallylation and propargylation of aldehydes with bis(((*S*)-binaphthoxy)(isopropoxy)titanium) oxide

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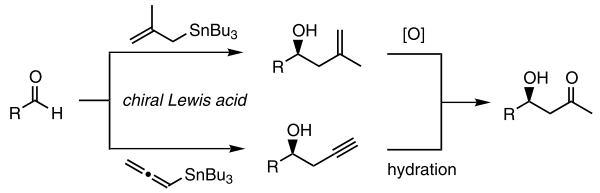
Abstract—New and highly efficient enantioselective methallylation and propargylation of achiral aldehydes with methallyltributyltin and allenyltributyltin, respectively, can be achieved with high enantioselectivity under the influence of chiral bis(((*S*)-binaphthoxy)(isopropoxy)titanium) oxide as catalyst.

1. Introduction

The enantioselective methallylation and propargylation of achiral aldehydes are important asymmetric transformations in organic synthesis,[1] and subsequent oxidative cleavage of the methallyl moiety and Hg(II)-promoted hydrolysis of the propargyl moiety provide optically active aldol products (Scheme 1), which are equivalent to those of asymmetric crossed aldol reactions between aldehydes and the enolate of acetone. In contrast to the numerous examples of catalytic asymmetric allylation of prochiral aldehydes with allyltributyltin,[2] the corresponding asymmetric methallylation and propargylation are rather difficult.[3,4] Indeed, compared to the allylic system, both reactivity and enantioselectivity in the catalytic asymmetric methallylation using ordinary chiral Lewis acid catalysts and methallyltributyltin were somewhat low, and did not exhibit broad applicability.[5] In addition, such transformations required longer reaction times at low temperature. Moreover, there have been few reports on the catalytic asymmetric propargylation of aldehydes using allenyltributyltin, presumably due to its low reactivity and regiochemical problems.[6]



Scheme 1.

2. Results

The requisite binaphthyl-modified bis-Ti(IV) oxide (*S*,*S*)-**1** was synthesized starting from triisopropoxytitanium chloride, $(Pr^iO)_3TiCl$ as described previously.[7,8] Thus, reaction of $(Pr^iO)_3TiCl$ (2 equiv.) with silver(I) oxide in CH_2Cl_2 at room temperature for 5 h gave rise to bis(triisopropoxy)titanium oxide, which was further treated with (*S*)-binaphthol (2 equiv.) at room temperature for 2 h to produce bis(((*S*)-binaphthoxy)(isopropoxy)titanium) oxide (*S*,*S*)-**1**. Reaction of hydrocinnamaldehyde **3** ($R = CH_2CH_2Ph$) with methallyltributyltin (1.1 equiv.) under the influence of in situ generated chiral bis-Ti(IV) oxide (*S*,*S*)-**1** (10 mol%) in CH_2Cl_2 at 0°C for 30 min afforded 5-methyl-1-phenyl-5-hexen-3-ol **4** ($R = CH_2CH_2Ph$) in 63% yield with 94% ee.[9] The absolute configuration of the homomethallylic alcohol was determined to be (*R*) by correlation with an authentic sample.[3b] 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 **2** (20 mol%), which is derived from $Ti(OPr^i)_4$ and (*S*)-binaphthol according to the literature procedure.[10]

Other selected examples are listed in Table 1. Several characteristic features of the present methallylation follow: (1) the chiral bis-Ti(IV) oxide (*S*,*S*)-**1** is applicable to various types of aldehydes and exhibits uniformly high asymmetric induction as well as high chemical

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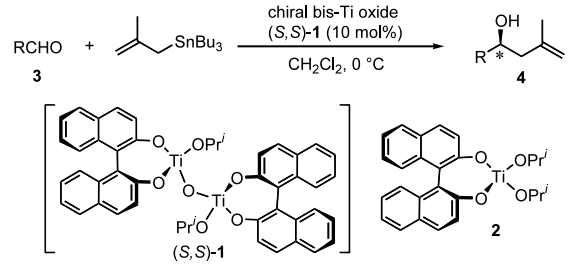
Table 1. Asymmetric methallylation of aldehydes with methallyltributyltin catalyzed by chiral bis-Ti(IV) oxide (*S*,*S*)-**1**[a]

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

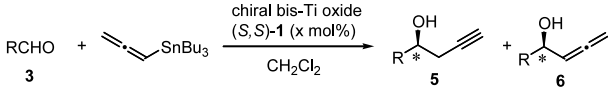
[a] Unless otherwise noted, the reaction of aldehyde and $Bu_3SnCH_2C(Me)=CH_2$ (1.1 equiv.) was carried out in the presence of chiral bis-Ti(IV) oxide (*S*,*S*)-**1** or chiral mono-Ti(IV) **2** in CH_2Cl_2 (0.33 M) at 0°C under the given reaction time.
[b] Isolated yield.
[c] Determined by HPLC analysis using Chiralcel OD, OD-H and OB-H.
[d] Determined by comparison of the sign of the specific rotation with reported values. See Ref. 3b.

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 methallylation compared to the corresponding mono-Ti(IV) catalyst **2**. (3) The absolute configuration of the homomethallylic alcohol **4** is predictable based on the use of either (*S*,*S*)-**1** or (*R*,*R*)-**1** (Scheme 2).



Scheme 2.

We further examined the reaction conditions of the asymmetric methallylation of aldehydes with (*S*,*S*)-**1**, and found some effect with the concentration of the substrate. Selected results are summarized in Table 2, which clearly shows a high dilution effect in correlating the enantiopurity of methallylation products **4** (R = CH_2CH_2Ph, CH = CHPh).



The present asymmetric approach can also be applied to the asymmetric propargylation of aldehydes with allenyltributyltin in the presence of chiral bis-Ti(IV) catalyst (*S*,*S*)-**1** as shown in Table 3.

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Table 2. Dilution effects of aldehyde substrate on the asymmetric methallylation of aldehydes with methallyltributyltin catalyzed by chiral bis-Ti(IV) oxide (*S*,*S*)-**1**[a]

Entry	Aldehyde	Concentration of substrate (M)	Reaction conditions (°C, h)	% Yield[b]	% ee[c] (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 of 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*)-**1** (10 mol%) in CH_2Cl_2 under the given reaction condition.
[b] Isolated yield.
[c] Determined by HPLC analysis using Chiralcel OD, OD-H and OB-H.

Table 3. Asymmetric propargylation of aldehydes with allenyltributyltin catalyzed by chiral bis-Ti(IV) oxide (*S*,*S*)-**1**[a]

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

[a] Unless otherwise noted, the reaction of aldehyde and $Bu_3SnCH{=}C{=}CH_2$ (1.1 equiv.) was carried out in the presence of chiral bis-Ti(IV) oxide (*S*,*S*)-**1** in CH_2Cl_2 (0.33 M) under the given reaction condition.
[b] Isolated yield.
[c] Isomeric ratio of homopropargyl alcohol **5** and homoallenyl alcohol **6**.
[d] Determined for major **5** by HPLC analysis using Chiralcel OD, OD-H and AD-H.
[e] Determined by comparison of the sign of specific rotation with reported values. See Ref. 4b.
[f] Use of excess $Bu_3SnCH{=}C{=}CH_2$ (3 equiv.).

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5. For example, catalytic asymmetric methallylation of cinnamaldehyde with BINOL-Ti(IV) complex at −20°C for 12 h gave 68% yield with 87% ee, while catalytic asymmetric methallylation of hydrocinnamaldehyde with BINAP–AgOTf complex at −20°C for 8 h afforded 22% yield with 70% ee. See Refs. 3a and 3f.
6. For example, catalytic asymmetric propargylation of aldehydes with BINOL-Ti(IV) complex requires 50∼100 mol% of the catalyst with very long reaction time (72∼100 h at −20°C) (Ref. 4a). Use of a stoichiometric amount of Et_2BSPr^i is reported to accelerate such asymmetric propargylations (Refs. 4b,c).
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