New Chiral Bis-Titanium(IV) Catalyst with Dibenzofuran Spacer for Catalytic Asymmetric Allylation of Aldehydes and Aryl Ketones

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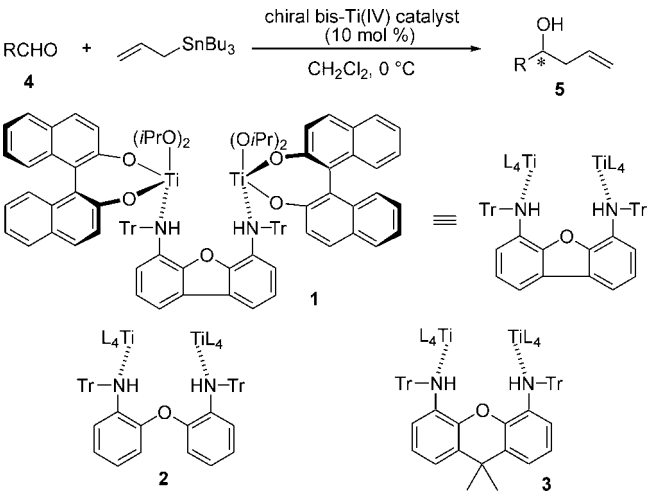
Catalytic asymmetric allylation of aldehydes has been considered as one of the most fundamental and important synthetic operations in asymmetric synthesis,[1,2] and a number of catalytic procedures have recently been elaborated for this purpose.[3–6] However, previously reported catalytic allylation processes generally exhibited less satisfactory results in enantioselectivity (~90% ee) in the case of cinnamaldehyde. In this context, we were interested in the possibility of introducing a new type of metal catalyst to improve the enantioselectivity in the asymmetric allylation of cinnamaldehyde with allyltributyltin. Herein we report the design of a new, chiral bis-Ti(IV) complex of the type **1**, and its utilization for the enantioselective allylation of aldehydes with allyltributyltin as illustrated in Scheme 1. In addition, this catalyst is also applicable to the catalytic, enantioselective allylation of aryl ketones.



Scheme 1. Catalytic asymmetric allylation of aldehyde **4** with allyltributyltin in the presence of the chiral bis-Ti(IV) complexes **1–3** [L_4 = ((*S*)-binaphthoxy)(O*i*Pr)$_2$]

The requisite spacers, 4,6-bis(tritylamino)dibenzofuran, 2,2′-bis(tritylaminophenyl) ether, and 4,5-bis(tritylamino)-9,9-dimethylxanthene can be easily prepared from commercially available dibenzofuran, diphenyl ether, and 9,9-dimethylxanthene, respectively, by the following sequence: (i) treatment of the diphenyl ether derivatives with BuLi/TMEDA (3 equiv) in ether/THF and subsequent addition of *p*-TsN_3 (60–77%); (ii) reduction of the bis-azides with $LiAlH_4$ in THF (85–95%); (iii) tritylation of diamines with NaH/TrBr (2.4 equiv) in THF (35–94%). Then, the series of chiral bis-Ti(IV) catalysts **1–3** is synthesized by mixing of these spacers with Ti(O*i*Pr)$_4$ (20 mol %) in CH_2Cl_2 at room temperature for 1 h and subsequent treatment with (*S*)-binaphthol (20 mol %) at room temperature for 10 h. The chiral efficiency of the bis-Ti(IV) catalysts **1–3** thus obtained, was evaluated by the enantioselective allylation of cinnamaldehyde, a rather tough substrate for conventional catalytic procedures.[3–6] Thus, reaction of cinnamaldehyde **4** (R = CH=CHPh) with allyltributyltin (1.1 equiv) under the influence of *in situ* generated chiral bis-Ti(IV) catalyst **1** (10 mol %) in CH_2Cl_2 at 0 °C for 10 h gave rise to 1-phenyl-1,5-hexadien-3-ol **5** (R = CH=CHPh) in 83% yield with 96% ee.[7,8] In a similar manner, the chiral bis-Ti(IV) catalysts **2** and **3** gave comparable results (85%, 96% ee with **2**; 81%, 96% ee with **3**), as indicated in Table 1. Notably, both the reaction rate and the enantioselectivity of the allylation are dramatically lowered (e. g., 8% and 85% ee for cinnamaldehyde) under similar reaction conditions with a chiral mono-Ti(IV) complex **6** derived from Ti(O*i*Pr)$_4$, (*S*)-binaphthol, and 4-(tritylamino)dibenzofuran as monodentate ligand (each 10 mol %). The chiral mono-Ti(IV) complex **7** (10 mol %) also gave less satisfactory result (17% and 92% ee for cinnamaldehyde).

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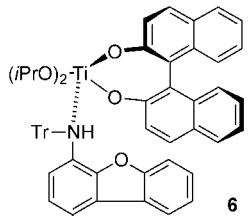
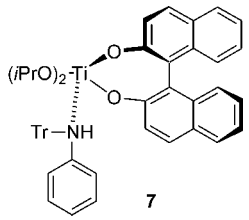




Other selected examples are included in Table 1. The chiral bis-Ti(IV) catalyst **1** generally exhibits higher reactivity than the analogues **2** and **3** (entries 4–6 and 7–9).

Although the exact reaction mechanism is not clear at present, one possibility involves the simultaneous coordination of two Ti atoms to a carbonyl oxygen, thereby allowing the double activation of the aldehyde carbonyls.[9,10] Such a double coordination phenomenon of the bis-Ti(IV) catalyst **1** can probably be deduced from the difference NOE measurement with *trans*-4-methoxy-3-buten-2-one at low temperature (–20 °C), where the enone conformation around the single bond can be determined. The free *trans*-4-methoxy-3-buten-2-one exists in both *s-cis* and *s-trans* conformations, (**A**) and (**B**), since irradiation of the

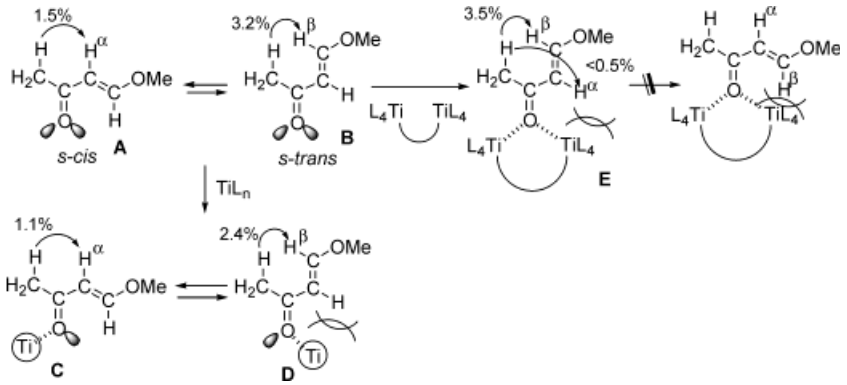
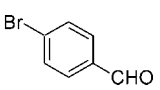
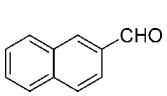


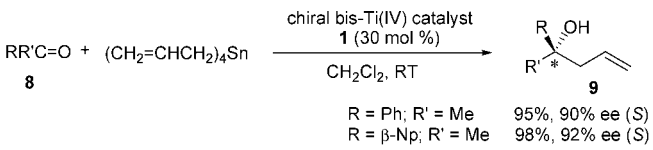
Table 1. Asymmetric allylation of aldehydes with allyltributyltin catalyzed by chiral bis-Ti(IV) complexes **1**–**3**[a]

entry	aldehyde	catalyst	conditions (°C, h)	% yield[b]	% ee[c] (config)[d]
1	PhCH=CHCHO	**1**	0, 10	83	96 (*S*)
2	”	**2**	0, 10	85	96 (*S*)
3	”	**3**	0, 10	81	96 (*S*)
4	PhCHO	**1**	0, 2.5	94	98 (*S*)
5	”	**2**	0, 2.5	67	97 (*S*)
6	”	**3**	0, 2.5	71	97 (*S*)
7		**1**	0, 10	96	99 (*S*)[e]
8	”	**2**	0, 10	81	98 (*S*)[e]
9	”	**3**	0, 10	84	98 (*S*)[e]
10	$PhCH_2CH_2CHO$	**1**	0, 3	90	97 (*S*)[f]
11		**1**	0, 8	88	96

[a] Unless otherwise noted, the reaction of aldehyde and $Bu_3SnCH_2CH=CH_2$ (1.1 equiv) was carried out in the presence of 10 mol % of chiral bis-Ti(IV) catalysts **1**–**3** in CH_2Cl_2 under the given reaction conditions.
[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. [4b]
[e] Correlated to (*S*)-**5** (R = Ph) (entries 4–6) by debromination of **5** (R = *p*-bromophenyl) with BuLi in ether.
[f] Correlated to (*S*)-**5** (R = CH=CHPh) (entries 1–3) by the catalytic hydrogenation of **5** (R = CH_2CH_2Ph) with Pd/C and H_2 to 1-phenyl-3-hexanol.

CH_3C=O protons resulted in moderate NOE to both α- and β-methoxyvinyl protons. On complexation with the mono-Ti(IV) Lewis acid **6**, irradiation of the CH_3C=O protons again resulted in similar NOE to both α- and β-methoxyvinyl protons. This result implies that both *s-cis* and *s-trans* conformers, (**C**) and (**D**) exist in a similar ratio to the free enone in solution. In contrast, however, in the bis-Ti(IV) **1**/enone complex, irradiation of the methyl proton of the enone resulted in moderate NOE to only the β-proton of the *trans*-methoxyvinyl group, implying the existence of the *s-trans* conformer (**E**) predominantly because of the double coordination.

The present approach can be successfully applied to the catalytic, enantioselective allylation of aryl ketones,[11] where we utilized tetraallyltin as a more effective allylation agent than allyltributyltin. For example, treatment of acetophenone **8** (R = Ph, R′ = Me) with tetraallyltin (1.5 equiv) under the influence of *in situ* generated chiral bis-Ti(IV) catalyst **1** (30 mol %) in CH_2Cl_2 at room temperature for 2.5 h gave rise to (*S*)-2-phenyl-4-penten-2-ol **9** (R = Ph, R′ = Me) in 95% yield with 90% ee.[12,13] Under similar conditions, methyl β-naphthyl ketone **8** (R = β-Np, R′ = Me) was transformed to (*S*)-2-β-naphthyl-4-penten-2-ol **9** (R = β-Np, R′ = Me) in 98% yield with 92% ee (Scheme 2).[14]



Scheme 2.

Experimental Section

Catalytic Asymmetric Allylation of Benzaldehyde with Allyltributyltin in the Presence of Bis-Ti(IV) Catalyst 1

A solution of 4,6-bis(tritylamino)dibenzofuran (341.4 mg, 0.5 mmol) in CH_2Cl_2 (15 mL) was carefully degassed and then treated with Ti(O*i*Pr)$_4$ (295 μL, 1.0 mmol) at room temperature under argon. After 1 h, (*S*)-BINOL (286.3 mg, 1.0 mmol) was added at room temperature, and the mixture was stirred for 10 h. The solution was then cooled to –15 °C, and treated sequentially with benzaldehyde (508 μL, 5 mmol) and allyltributyltin (1.71 mL, 5.5 mmol) at –15 °C. The whole mixture was allowed to warm to 0 °C and stirred for 2.5 h. The reaction mixture was quenched with saturated $NaHCO_3$, and extracted with CH_2Cl_2. The organic extracts were dried over Na_2SO_4. Evaporation of the solvents and purification of the residue by column chromatography on silica gel (ether/hexane = 1 : 4) gave (*S*)-1-phenyl-3-buten-1-ol as a colorless oil; yield: 696.5 mg (94%). (*S*)-BINOL and 4,6-bis(tritylamino)dibenzofuran were recovered in 89% and 74% yields, respectively.[15]

The absolute configuration and enantiomeric purity of 1-phenyl-3-buten-1-ol were determined to be *S* and 98% ee by analytical HPLC analysis [Daicel Chiralcel OD, hexane/*i*PrOH = 30 : 1, flow rate = 0.5 mL/min, *t*R = 21.48 min ((*R*)-isomer), *t*R = 26.21 min ((*S*)-isomer)] in comparison with the racemic and authentic samples.[4b]

Acknowledgments

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[7] The absolute configuration of the homoallylic alcohol **5** (R = CH=CHPh) was determined to be *S* by correlation to the authentic sample; see ref. [4b].

[8] Our initial attempt to use chiral bis-Ti(IV) catalysts of type **1** (10 mol %) from the parent 4,6-diaminodibenzofuran or 4,6-bis(ethylamino)dibenzofuran as spacers by combining $Ti(OiPr)_4$ and chiral (*S*)-binaphthol turned out to be less satisfactory [15% (90% ee) or 12% yield (85% ee), respectively, at 0 °C for 10 h] in the asymmetric allylation of cinnamaldehyde **4** (R = CH=CHPh) with allyltributyltin. Introduction of bulky silyl moieties on the amino groups in 4,6-diaminodibenzofuran in order to make two Ti atoms closely aligned by their steric repulsion resulted in enhancement of reactivity of the asymmetric allylation. Indeed, the bis-Ti(IV) catalyst (10 mol %) of type **1** derived from 4,6-bis(*t*-butyldiphenylsilylamino)dibenzofuran, $Ti(OiPr)_4$, and (*S*)-binaphthol afforded **5** (R = CH=CHPh) in 34% yield (93% ee) (at 0 °C for 10 h).

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[10] Such activation is also observed by ^{13}C NMR spectroscopy using 2,6-dimethyl-γ-pyrone as carbonyl substrate: ^{13}C NMR ($CDCl_3$ at 20 °C): δ = 165.41 (free pyrone β-carbons); 166.31 (pyrone β-carbons of the 1:1 2,6-dimethyl-γ-pyrone/mono-Ti(IV) **6** complex), 167.46 (pyrone β-carbons of the 1:1 2,6-dimethyl-γ-pyrone/bis-Ti(IV) **1** chelation complex), 166.39 (pyrone β-carbons of the 2:1 2,6-dimethyl-γ-pyrone/bis-Ti(IV) **1** chelation complex).

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[12] Attempted allylation of acetophenone **8** (R = Ph, R′ = Me) with allyltributyltin (1.5 equiv) in the presence of *in situ* generated chiral bis-Ti(IV) catalyst **1** (30 mol %) in CH_2Cl_2 gave none of 2-phenyl-4-penten-2-ol **9** (R = Ph, R′ = Me) with recovery of most of the acetophenone under similar conditions.

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[14] In the asymmetric allylation of ketones with tetraallyltin, the enantioselectivity tends to be lowered by decreasing the amount of the bis-Ti(IV) catalyst **1** [e. g., 90% (30 mol % **1**); 76% (20 mol % **1**); 66% (10 mol % **1**) with acetophenone], probably because of the undesired intervention of the *in situ* generated, more reactive triallyltin alkoxide (or diallyltin dialkoxide) than tetraallyltin during the course of the ketone allylation.

[15] 6-Amino-4-(tritylamino)dibenzofuran was also recovered in 17% yield.