

Bidentate Lewis acid catalysts in asymmetric synthesis*

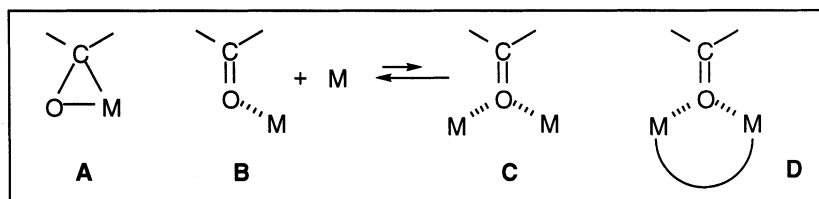
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Abstract: The chemistry of bidentate Lewis acids belongs to an unexplored field of science, and so far has been only poorly studied. This paper illustrates the design of several bidentate Al and Ti Lewis acids, and their successful application to selective organic synthesis, particularly to asymmetric synthesis. For example, a new, chiral bidentate Ti(IV) complex is successfully designed by adding commercially available $\text{Ti}(\text{OPr}^i)_4$ and (*S*)-binaphthol sequentially to 2,2'-bis(tritylamino)-4,4'-dichlorobenzophenone in CH_2Cl_2 , and can be utilized for simultaneous coordination to aldehyde carbonyls, thereby allowing the precise enantioface discrimination of such carbonyls for a new catalytic, practical enantioselective allylation of aldehydes with allyltributyltin. This chiral bidentate Ti(IV) catalyst exhibits uniformly high asymmetric induction as well as high chemical yields for various aldehydes. The present enantioselective allylation is highly chemoselective in the presence of other carbonyl moieties.

INTRODUCTION

Electrophilic activation of carbonyl groups with certain Lewis acids is a well-established method for enhancing their reactivity and selectivity toward nucleophilic addition. The two principal modes of coordination of carbonyls to metals are the π -bonding (**A**) and σ -bonding (**B**) [1,2]. The latter mode is generally preferred with main-group and early-transition-metal Lewis acids. In addition, simultaneous coordination to carbonyl groups with two metals of type (**C**) would alter the reactivity and selectivity of the carbonyl substrates. Examples of such double coordination with two metals are rare despite its potential importance, simply because of the high preference for the single coordination mode (**B**) even in the presence of excess Lewis acids, and hence the nature of such di- σ -bonding (**C**) remains elusive [3]. In this context, we have been interested in the possibility of designing bidentate Lewis acids that are capable of preferable di- σ -bonding (**D**) with two metals by using certain spacers [4–6]. Among various main-group and early-transition-metal elements, aluminium and titanium seem to be the metals of choice in view of their high affinity toward oxygen atom [7–11]. Accordingly, we set out our study on

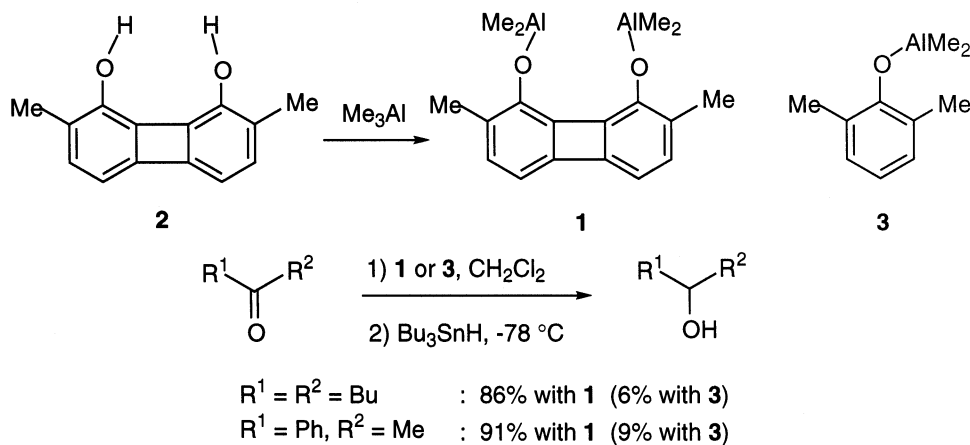


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this subject by using modified bis(aluminium) reagents for the efficient simultaneous coordination toward carbonyls, thereby elucidating the characteristics of the double electrophilic activation of carbonyl substrates.

BIDENTATE ALUMINIUM LEWIS ACID

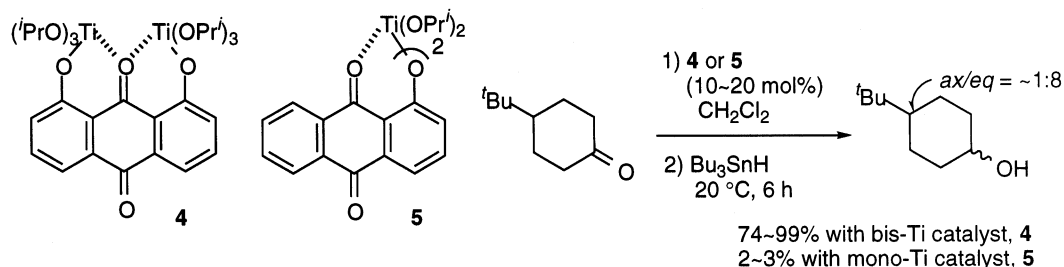
The requisite bidentate ligand, 2,7-dimethyl-1,8-biphenylenediol (**2**) for the design of a bidentate aluminium Lewis acid was synthesized according to the literature procedure [12], and the bidentate organoaluminium reagent, (2,7-dimethyl-1,8-biphenylenedioxy)-bis(dimethylaluminium) (**1**) was prepared by treatment of the biphenylenediol **2** with Me_3Al (2 equiv) in CH_2Cl_2 at room temperature [13–15]. Initial complexation of 5-nonanone with the *in situ* generated **1** (1.1 equiv) in CH_2Cl_2 and subsequent reaction of Bu_3SnH (1.2 equiv) at -78°C for 20 min gave rise to the corresponding 5-nonanol in 86% yield. In marked contrast, however, reduction of 5-nonanone with Bu_3SnH in the presence of monodentate organoaluminium reagent **3** [prepared from 2,6-xyleneol and Me_3Al (1:1 molar ratio)] under similar reaction conditions afforded 5-nonanol in very low yield. These results clearly demonstrate that the bidentate Lewis acid **1** strongly enhances the reactivity of ketone carbonyl toward hydride transfer via the double electrophilic activation of carbonyl moiety. It should be noted that reduction of excess 5-nonanone (2 equiv) with bidentate **1** (1.1 equiv)/ Bu_3SnH (2.2 equiv) in CH_2Cl_2 at -78°C for 20 min lowered the yield of 5-nonanol (47%), suggesting the intervention of the 1:1 ketone/Lewis acid complex even in the presence of excess ketone. Furthermore, use of excess **3** (2 equiv) for 1 equiv of 5-nonanone resulted in formation of 5-nonanol in 10% yield, implying the favorable monocoordination complex (**B**) even in the presence of excess Lewis acids. A similar tendency is observed in the acetophenone carbonyl reduction.



BIDENTATE TITANIUM LEWIS ACID

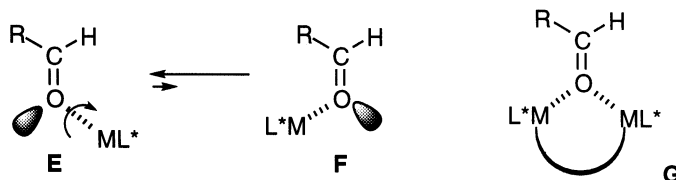
In contrast to the aluminium Lewis acids, titanium Lewis acids are easily employable as catalyst rather than stoichiometric Lewis acids. Accordingly, bidentate titanium catalyst of type **4** was prepared by mixing commercially available 1,8-dihydroxyanthraquinone with a feeble Lewis acid, $\text{Ti}(\text{OPr}^i)_4$ (2 equiv) in CH_2Cl_2 at 25°C [16]. The simultaneous coordination of two titanium atoms to one anthraquinone carbonyl is verified by ^{13}C NMR analysis of the bidentate titanium catalyst **4**. Similarly, the corresponding monodentate titanium catalyst **5** was obtained from 1-hydroxyanthraquinone and $\text{Ti}(\text{OPr}^i)_4$, though 2 equiv of 1-hydroxyanthraquinone is replaced by isopropoxy ligands in this particular case. Complexation of 4-*tert*-butylcyclohexanone with the *in situ* generated bidentate titanium catalyst **4** (10–20 mol%) in CH_2Cl_2 and subsequent treatment with Bu_3SnH (1.1 equiv) at -20°C and at 20°C for 6 h afforded 4-*tert*-butylcyclohexanol in 74–99% yield. In marked

contrast, however, reduction of 4-*tert*-butylcyclohexanone with monodentate titanium catalyst **5** (10~20 mol%) under otherwise similar reduction conditions gave 4-*tert*-butylcyclohexanol in only 2~3% yield. Further, use of $\text{Ti}(\text{OPr}^i)_4$ resulted in total recovery of the starting ketone. These results clearly demonstrate that the bidentate Ti catalyst **4** strongly enhances the reactivity of ketone carbonyl toward hydride transfer via the double electrophilic activation of carbonyl moiety.

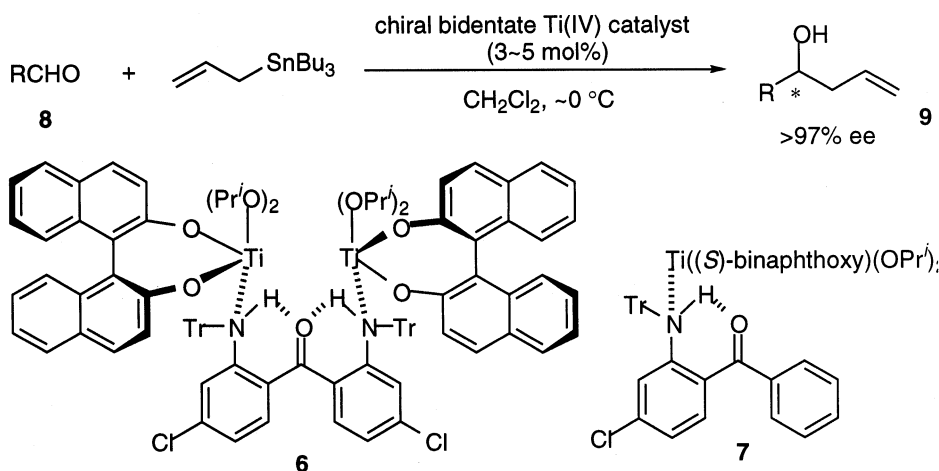


CHIRAL BIDENTATE TITANIUM LEWIS ACID

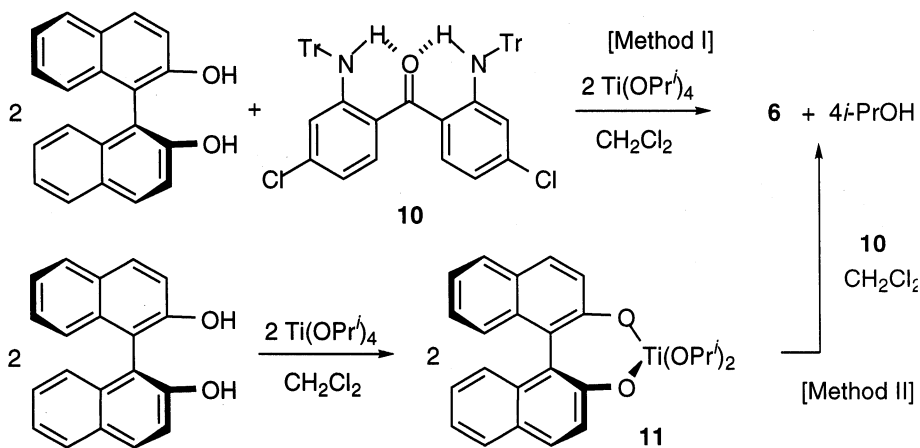
With the basic information on the bidentate Lewis acid chemistry at hand, our attention has now been focused on the asymmetric catalytic synthesis with chiral, bidentate Ti Lewis acid catalysts. As one of the fundamental yet powerful C–C bond-forming reactions, enantioselective allylation of aldehydes attracts considerable attention in asymmetric synthesis. Given the versatile chemistry of the resulting homoallylic alcohols, this asymmetric transformation constitutes a valuable process [17,18]. Despite considerable recent progress in this area using both stoichiometric and catalytic amounts of chiral Lewis acids, continuing improvements in the efficiency of these Lewis acids have been made within the field of asymmetric catalysis. In this respect, a most practical catalytic allylation should utilize an inexpensive and readily available chiral ligand, and provide uniformly high and predictable enantioselectivity across a wide range of aldehyde substrates. For instance, in the case of cinnamaldehyde, previously reported catalytic processes generally exhibited less-satisfactory enantioselectivity (up to ~90% ee). This is mainly because previous strategies utilize a single coordination complex **E** between aldehyde and chiral monodentate Lewis acids which inevitably causes free rotation at the M–O bond, and the *anti*-coordination **F** of a Lewis acid (ML^*) toward aldehyde would also decrease the enantioselection compared to the unfavorable *syn*-coordination **F**. In order to overcome these intrinsic problems by the approaches currently known, we are interested in the possibility of forming double coordination complex **G** with chiral bidentate Lewis acids, thereby allowing more precise enantioface discrimination of aldehyde carbonyl. Here we designed a new chiral bidentate Ti(IV) complex of type **6** for a new catalytic, practical enantioselective allylation of aldehydes with allyltributyltin as shown in Scheme 1 [19].



The design of chiral bidentate Ti(IV) catalysts originates from our achiral bidentate Lewis acid chemistry [13–16]. Accordingly, the chiral bidentate catalyst **6** is prepared by mixing of 2,2'-bis(tritylamino)-4,4'-dichlorobenzophenone **10** (5 mol%) with $\text{Ti}(\text{OPr}^i)_4$ (10 mol%) in CH_2Cl_2 at room temperature for 1 h and subsequent treatment with (*S*)-binaphthol (10 mol%) at room temperature for 15 h [Method I in Scheme 2]. Reaction of benzaldehyde with allyltributyltin (1 equiv) under the influence of



Scheme 1



Scheme 2

in situ generated chiral bidentate catalyst **6** (5 mol%) in CH_2Cl_2 at $0\text{ }^\circ C$ for 2 h gave rise to 1-phenyl-3-buten-1-ol **9** ($R = Ph$) in 95% yield with 99% ee. The absolute configuration of the homoallylic alcohol was determined to be *S* by correlation to the authentic sample. The amount of the catalyst **6** can be reduced to 3 mol% with similar chemical yield and enantioselectivity (96% yield, 98% ee) except for the need of longer reaction time as shown in Table 1 (entry 1).

The chiral bidentate catalyst **6** can be also prepared from $Ti[(S)\text{-binaphthoxy}](OPr^i)_2$ (**11**) and **10** in CH_2Cl_2 [Method II in Scheme 2]. This *i*-PrOH-free catalyst **6** is more reactive than the *in situ* generated chiral catalyst **6**, and the asymmetric allylation with the *i*-PrOH-free catalyst **6** (5 mol%) proceeded at $-20\text{ }^\circ C$ for 2 h to furnish homoallylic alcohol **9** ($R = Ph$) in 85% yield with 98% ee (entry 4). It should be noted that both the reaction rate and the enantioselectivity of the allylation are much lowered (e.g., 9% and 90% ee for benzaldehyde) under similar reaction conditions with a chiral monodentate Ti(IV) complex **7** derived from $Ti(OPr^i)_4$, (*S*)-binaphthol, and 4-chloro-2-(tritylamino)benzophenone as monodentate ligand (each 5 mol%). In addition, a chiral, *in situ* generated $Ti[(S)\text{-binaphthoxy}](OPr^i)_2$ (**11**) (5 mol% or 10 mol%) from $Ti(OPr^i)_4$ and (*S*)-binaphthol tremendously

Table 1 Asymmetric allylation of aldehydes with allyltributyltin catalyzed by chiral bidentate Ti(IV) complex **6**^a.

Entry	Aldehyde	Catalyst ^b (mol%)	Condition (°C, h)	% Yield	% ee (config.)
1	PhCHO	[A] (3)	0, 5	96	98 (S)
2		[A] (5)	0, 2	95	99 (S)
3		[B] (3)	-15, 15	74	97 (S)
4	CH ₃ (CH ₂) ₆ CHO	[B] (5)	-20, 2	85	98 (S)
5		[A] (5)	0, 12	82	97 (R)
6		[B] (3)	0, 2	75	98 (R)
7	(CH ₃) ₂ CHCHO	[B] (5)	0, 0.5	88	99 (R)
8		[A] (5)	0, 24	54	98 (S)
9		[B] (5)	0, 1	77	>99 (S)
10	PhCH ₂ CH ₂ CHO	[A] (3)	0, 4	89	97 (R)
11		[A] (5)	0, 2	83	98 (R)
12		[B] (3)	-10, 12	71	98 (R)
13	PhCH=CHCHO	[A] (10)	0, 10	79	97 (S)
14		[B] (5)	0, 5	88	97 (S)
15	2-naphthaldehyde	[A] (5)	0, 10	92	98
16		[B] (3)	0, 6	99	97
17	furfural	[A] (3)	0, 5	85	97
18		[B] (3)	0, 2	88	95

^aUnless otherwise noted, the reaction of aldehyde and Bu₃SnCH₂CH=CH₂ (1 equiv) was carried out with chiral bidentate Ti(IV) catalyst **6** (3~5 mol%) in CH₂Cl₂ under the given reaction conditions.

^bCatalyst [A] refers to the *in situ* generated **6** by Method I. Catalyst [B]: *i*-PrOH-free catalyst **6** by Method II.

retarded the allylation, giving homoallylic alcohol **9** (R = Ph) in only 3% yield (71% ee) or 5% yield (72% ee).

As revealed in Table 1, several characteristic features of the present allylation have been noted: (1) The chiral bidentate Ti(IV) catalyst **6** exhibits uniformly high asymmetric induction as well as high chemical yield. As a general tendency, the *i*-PrOH-free catalyst **6** is more reactive than the *in situ* generated **6**, and the asymmetric allylation with the *i*-PrOH-free catalyst **6** (3~5 mol%) proceeds at lower or similar reaction temperature with shorter reaction time. (2) The simultaneous coordination and double activation ability of the bidentate Ti(IV) catalyst **6** toward aldehyde carbonyls strongly accelerated the rate of allylation compared to ordinary BINOL-Ti(OPr^{*i*})₄ complexes. (3) The enantioselectivity of the present allylation is not sensitive to the reaction temperature (i.e., 98~99% ee at -15~20 °C in the case of benzaldehyde). (4) This asymmetric procedure is operationally quite simple. Thus, commercially available Ti(OPr^{*i*})₄ and chiral binaphthol are sequentially added to 2,2'-bis(tritylamino)-4,4'-dichlorobenzophenone **10** in CH₂Cl₂ at room temperature to generate the requisite catalyst **6**, which is then treated with aldehyde **8** and allyltributyltin at 0 °C for several hours.

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