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# Enantioselective addition of AlEt<sub>3</sub> to aldehydes catalyzed by titanium(IV)–TADDOLate complex

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## Abstract

Enantioselective addition of AlEt<sub>3</sub> to aldehydes catalyzed by a titanium(IV)–TADDOLate complex was carried out with ee values up to 99% for 2-chlorobenzaldehyde as a substrate. The key success of the study resides in the choice of THF as a solvent. THF is capable of coordinating to Al(III) and is speculated to lower the Lewis acidity of AlEt<sub>3</sub> and thus to suppress the competing reaction from AlEt<sub>3</sub> itself.  $\bigcirc$  2000 Elsevier Science Ltd. All rights reserved.

## 1. Introduction

Asymmetric catalytic carbon–carbon bond formation has been one of the most studied reactions in the past 10 years.<sup>1</sup> Among these, the enantioselective additions of diethylzinc to aldehydes has gained much attention.<sup>2</sup> The most successful catalysts in these reactions have been titanium complexes which employ chiral diols<sup>3,4</sup> or bissulfonamides.<sup>5</sup> In general, the catalytic systems were prepared in situ by mixing chiral ligands with Ti(O-*i*-Pr)<sub>4</sub>. In terms of industrial applications, the asymmetric alkylation addition of trialkylaluminum to aldehydes for the preparation of enantiomerically pure secondary alcohols is very interesting for economic reasons due to the industrial bulk production of trialkylaluminum reagents.<sup>6</sup> However, to our knowledge, there were only two papers dealing with the asymmetric catalytic addition of trialkylaluminum to aldehydes. First, Chan et al. used BINOLs or BINOL derivatives mixed with excess Ti(O-*i*-Pr)<sub>4</sub> to catalyze ethylation of aldehydes and excellent enantioselectivities were obtained with ee values up to 96.4%.<sup>7</sup> In a recent report by Carreira, a mixture of roughly equal molar equiv. of TiF<sub>4</sub> (14 mol%) and *trans*-1,2-cyclohexanedimethanol (15 mol%) was used to catalyze methyl addition to various aldehydes with ee values up to 85%. Replacing *trans*-1,2-cyclohexanedimethanol with a TAD-DOL ligand, however, gave a low ee value of 32%.<sup>8</sup>

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Recently, we were interested in developing asymmetric alkylation reactions using trialkylaluminum reagents and thus, enantioselective ethylation of aldehydes catalyzed by Ti(IV)–TAD-DOLate complexes were carried out. Excellent enantioselectivities were obtained with ee values up to 99%.

## 2. Results and discussion

In this study, enantioselective additions of AlEt<sub>3</sub> to aldehydes catalyzed by Ti(IV)–TADDO-Late complexes were carried out (Eq. (1)) with results listed in Table 1. Entry 1 is a blank reaction without addition of the TADDOL ligand and Ti(O-i-Pr)<sub>4</sub> and the result shows that AlEt<sub>3</sub> itself reacts with aldehyde to afford 1-phenyl-propanol in a 65% conversion and a 27% yield. In entries 2-10, 10-20 mol% of TADDOL was used as a chiral diol ligand and 0.5 mmol of benzaldehyde was used as a substrate. In entry 2, the use of 1.20 mmol of Ti(O-i-Pr)<sub>4</sub> and 1.00 mmol of AlEt<sub>3</sub> gave nearly a quantitative yield of (S)-1-phenylpropanol with 73% ee. When AlEt<sub>3</sub> was increased to 1.25 mmol, the ee value increased slightly to 75% (entry 3). Keeping AlEt<sub>3</sub> at 1.25 mmol but increasing  $Ti(O-i-Pr)_4$  to 1.50 mmol, the ee value decreased slightly to 71% (entry 4). From entries 5 to 8, increasing both Ti(O-i-Pr)<sub>4</sub> and AlEt<sub>3</sub> increased ee values gradually and the best ee value was 84% with the use of 2.50 mmol of Ti(O-*i*-Pr)<sub>4</sub> and 2.50 mmol of AlEt<sub>3</sub> (entry 8) with a relative ratio of 1:25:25 for TADDOL:Ti(O-i-Pr)<sub>4</sub>:AlEt<sub>3</sub>. Further increasing both Ti(O-i-Pr)<sub>4</sub> and AlEt<sub>3</sub> to 3.00 mmol gave a lower ee value of 76% (entry 9). Reducing TADDOL, Ti(O-i-Pr)<sub>4</sub> and AlEt<sub>3</sub> to half of those in entry 8, a lower ee value of 68% was obtained (entry 10). It seems in this study that the enantioselectivities of the addition of  $AlEt_3$  to benzaldehyde is rather sensitive to variations of both Ti(O-i-Pr)<sub>4</sub> and AlEt<sub>3</sub>. Similar to the enantioselective addition of ZnEt<sub>2</sub> to aldehydes, a

Asymmetric addition of Alet <sub>3</sub> to benzaidenyde							
Entry	TADDOL (mol %)	Ti(O- <i>i</i> -Pr) <sub>4</sub> (mmol)	AlEt <sub>3</sub> (mmol)	Yield <sup>b</sup> (%)	ee <sup>c</sup> (%)	-	
1	-	-	1.25	27	-	-	
2	20	1.20	1.00	98	73		
3	20	1.20	1.25	99	75		
4	20	1.50	1.25	96	71		
5	20	2.00	1.25	99	73		
6	20	2.00	1.50	100	75		
7	20	2.00	2.00	99	78		
8	20	2.50	2.50	94	84		
9	20	3.00	3.00	93	76		
10	10	1.25	1.25	99	68		

Table 1 Asymmetric addition of AIEt, to benzaldehyde<sup>a</sup>

<sup>a</sup>Benzaldehyde, 0.5 mmol; THF, 1.5 mL; reaction time, 12 h. <sup>b</sup>Determined by <sup>1</sup>H NMR.

<sup>c</sup>Determined by HPLC with a chiral OD column from Daicel.

higher ratio of  $Ti(O-i-Pr)_4$  to chiral ligand is required in order to obtain better enantioselectivities.<sup>3–5</sup> In this study, the best ratio was determined to be 25 to 1.

The key factor for a successful practice of enantioselective addition of AlEt<sub>3</sub> to aldehydes, at least in this study, is the choice of solvent. For asymmetric catalytic addition of  $ZnEt_2$  to aldehydes, the most used solvent system is toluene and, in fewer cases, *n*-hexane or CH<sub>2</sub>Cl<sub>2</sub> is used. For coordinating solvent systems such as Et<sub>2</sub>O or THF, enantioselectivities are usually lower due to, presumably, competing coordination of solvent molecules for the metal center. However, in this study, choosing the non-coordinating solvent systems such as toluene, *n*-hexane, or CH<sub>2</sub>Cl<sub>2</sub>, gave

entry	Aldehyde	Yield <sup>b</sup> (%)	ee <sup>c</sup> (%)
1	С <sup>О</sup> н	94	84
2	Р	88	53
3	ССС <sup>Р</sup> н	96	86
4	CI CI H	99	79
5	CI H	98	99
6	MeO	91	79
7	O Me	97	43
8	C H	100	78

 Table 2

 Asymmetric addition of AlEt<sub>3</sub> to various aldehydes<sup>a</sup>

<sup>c</sup>Determined by HPLC with a chiral OD column from Daicel.

<sup>&</sup>lt;sup>a</sup>Benzaldehyde, 0.5 mmol; THF, 1.5 mL; reaction time, 12 h. <sup>b</sup>Determined by <sup>1</sup>H NMR.

the secondary alcohol without any enantioselectivity. In  $Et_2O$ , the reaction gave the product with 68% ee and, in THF, the ee values range from 68–84% for benzaldehyde as the substrate (Table 1). It is well known that coordinating solvent molecules may bond to an Al(III) metal center. Since AlEt<sub>3</sub> itself reacts with aldehydes resulting in lower enantioselectivities (entry 1), the coordination of THF to aluminum is expected to lower the Lewis acidity of AlEt<sub>3</sub> and thus suppress the competing reaction.



In order to study the generality of the catalytic asymmetric reactions, addition of AlEt<sub>3</sub> to various aldehydes was conducted in THF (Table 2). From Table 2, the yields are in general higher than 90% for a reaction time of 12 h and the ee values are good to excellent except in a couple of cases such as 53% ee for 1-naphthaldehyde as a substrate (entry 2) and 43% ee for *o*-methoxy-benzaldehyde (entry 7). The best ee values can be up to 99% for 2-chlorobenzaldehyde (entry 5) as a substrate. For non-aromatic aldehydes such as *trans*-cinnamaldehyde, the ee value is somewhat lower at 78% (entry 8). It seems that, for aromatic aldehydes with *ortho*-substituents such as a methoxy group, the reaction gave lower ee values due to steric hindrance of the *ortho* substitution. Yet, for aromatic aldehydes with an *ortho*-chloro group, the best ee value of 99% is obtained. In this case, *o*-chlorobenzaldehyde is capable of forming a chelate complex with the chiral titanium catalyst, thereby allowing a rigid transition structure for obtaining high ee.

In summary, enantioselective additions of AlEt<sub>3</sub> to various aldehydes were performed. Higher ratios of both  $Ti(O-i-Pr)_4$  and AlEt<sub>3</sub> relative to the chiral TADDOL ligand are required in order to obtain the best ee values. The catalytic reactions are very sensitive to the choice of solvent. In non-coordinating solvents such as toluene or CH<sub>2</sub>Cl<sub>2</sub>, the reactions give no enantioselectivities. In THF, however, enantioselectivities are good to excellent with the best ee value being 99% for 2-chlorobenzaldehyde as the substrate. The role of THF is speculated to lower the Lewis acidity of AlEt<sub>3</sub> thus suppressing the competing reaction from AlEt<sub>3</sub> itself.

## 3. Experimental

#### 3.1. Reagents and general techniques

 $\alpha, \alpha, \alpha', \alpha'$ -Tetraphenyl-1,3-dioxolane-4,5-dimethanol<sup>9</sup> (TADDOL) was prepared according to literature procedures. Ti(O-*i*-Pr)<sub>4</sub> was freshly distilled prior to use. Aldehydes were distilled or recrystallized before use. Solvents were dried by refluxing for at least 24 h over P<sub>2</sub>O<sub>5</sub> (dichloromethane) or sodium/benzophenone (*n*-hexane, THF, or toluene) and were freshly distilled prior to use. Deuterated chloroform was dried over molecular sieves. All manipulations were carried out under a dry dinitrogen atmosphere. The yield of the product is determined by <sup>1</sup>H NMR spectra on a Varian Mercury-400 (400 MHz) spectrometer. The enantiomeric purity of the product was determined by HPLC with a Chiralcel-OD column from Daicel.

## *3.2. General procedures for the addition of AlEt*<sub>3</sub> *to aldehydes*

Under dry dinitrogen atmosphere, the ligand and  $Ti(O-i-Pr)_4$  were mixed in 1.5 mL of dry THF at room temperature. After 1 h, AlEt<sub>3</sub> (1.9 M solution in toluene) was injected at 0°C. After the mixture was stirred for 30 min, the orange-colored solution was treated with aldehyde (0.5 mmol) at 0°C and stayed at this temperature for 10 h, and quenched with 1N HCl. The aqueous phase was extracted with ethyl acetate (3×5 mL), dried over MgSO<sub>4</sub>, filtered and concentrated. Chromatography of the residue on silica gel (elution with 5:1 hexane:ethyl acetate) gave the carbinol.

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