

# $\alpha$ -Hydroxy carboxylic acids as ligands for enantioselective addition reactions of organoaluminum reagents to aromatic and aliphatic aldehydes

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**Abstract**—The first examples of the enantioselective titanium-mediated trialkylaluminum additions to aromatic and aliphatic aldehydes catalyzed by optically active  $\alpha$ -hydroxy acids are presented. The reactions proceed with very good yields and in good asymmetric induction. Enantioselectivities up to 92% are obtained depending on the ligand and aldehyde used. A stereochemical model for the reaction is proposed.

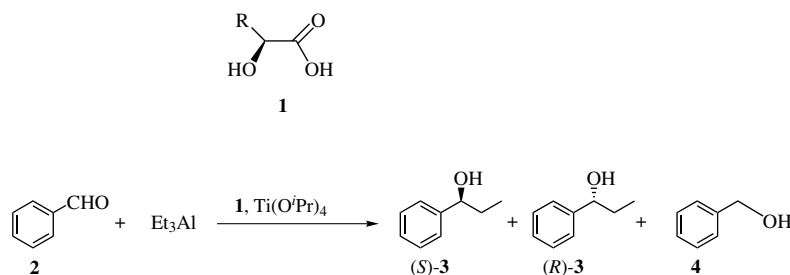
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## 1. Introduction

Enantioselective organometallic addition to aldehydes is a valuable method for the synthesis of optically active secondary alcohols and several efficient systems have been developed, asymmetric additions of organometallic reagents to aldehydes remains a challenge. Chiral secondary alcohols are often found in natural products, and are of great interest to the pharmaceutical industry. From the economic point of view, catalytic systems based on inexpensive chiral ligands and organometallic reagents available in bulk quantities can be very attractive provided that chiral product is obtained with good enantiomeric excess (better than 80%) and can be fur-

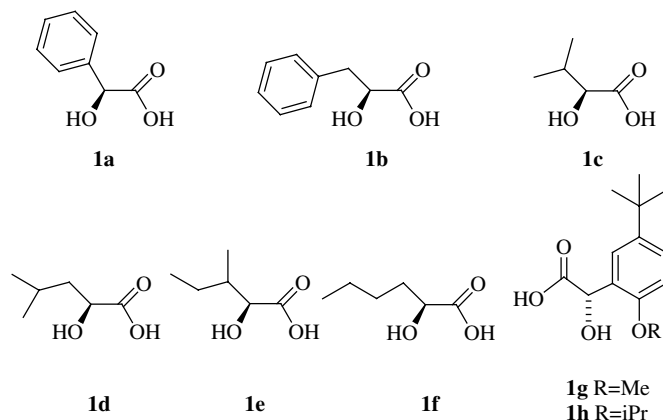
ther purified by crystallization. For industrial purposes, such a solution could be more interesting than the use of a ligand, which gives product with very high ee, but its synthesis is tedious and expensive (Scheme 1).

Recently, we have introduced new class of chiral ligands for enantioselective organometallic additions.  $\alpha$ -Hydroxy carboxylic acids are excellent ligands for the enantioselective addition of diethylzinc to aromatic and aliphatic aldehydes.<sup>1</sup> Taking into account the above discussed literature reports<sup>2–4</sup> we decided to investigate the additions of triethyl- and trimethylaluminum to aldehydes, catalyzed by  $\alpha$ -hydroxy carboxylic acids **1a–h** (Scheme 2).



Scheme 1.

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Scheme 2.

## 2. Results and discussion

### 2.1. Enantioselective triethylaluminum addition

**2.1.1. Enantioselective triethylaluminum addition to aldehydes in the presence of (*S*)-mandelic acid.** The first reaction was performed under conditions proposed by Chan et al.: 0.2 equiv of (*S*)-mandelic acid **1a** as the ligand, 1.4 equiv of  $\text{Ti}(\text{O}^i\text{Pr})_4$ , and 3 equiv of  $\text{Et}_3\text{Al}$  in THF at room temperature.<sup>2</sup> The reaction was stirred overnight, and after TLC showed complete conversion, quenched with aqueous hydrochloric acid. After work-up and chromatography 1-phenyl-1-propanol **3** was isolated in 85% yield. The enantiomeric excess [74% ee in favor of the (*1S*) product] was determined by HPLC using a Chiracel OD column.

To examine the effect of the solvent the reaction was carried out in five typical solvents. The best enantiomeric excess and yield were obtained for tetrahydrofuran (Table 1, entry 1), but the reaction was much slower than in other solvents. The fastest reaction was observed in toluene, but the product was obtained with low ee. We decided to test, whether the mixture of these two solvents (toluene/THF 1:1) can give better results, but the reaction appeared to be as slow as it was in THF and gave the product with moderate ee (Table 1, entry 6). For further experiments THF was chosen as the solvent.

We continued investigation of factors influencing yield and asymmetric induction in this reaction. The reaction performed in the absence of  $\text{Ti}(\text{O}^i\text{Pr})_4$  is slow and

Table 1.  $\text{Et}_3\text{Al}$  addition in various solvents

Entry	Ligand	Solvent	Temp [°C]	Time [h]	Yield [%]	Ee (config.) [%]
1	<b>1a</b>	THF	17	19	85	74 ( <i>S</i> )
2	<b>1a</b>	<i>n</i> -Hexane	28	3	83	10 ( <i>S</i> )
3	<b>1a</b>	Ether	28	2.5	86	10 ( <i>S</i> )
4	<b>1a</b>	$\text{CH}_2\text{Cl}_2$	18	4	34	3 ( <i>R</i> )
5	<b>1a</b>	Toluene	28	2.5	86	11 ( <i>S</i> )
6	<b>1a</b>	Toluene/THF	19	19	96	62 ( <i>S</i> )

Table 2. Influence of various parameters on the addition of  $\text{Et}_3\text{Al}$  to benzaldehyde

Entry	Ligand	Amount [equiv]	Concn [mmol/mL]	Temp [°C]	Time [h]	Yield [%]	Ee (config.) [%]
1 <sup>a</sup>	<b>1a</b>	0.2	0.04	27	27	88	14 ( <i>R</i> )
2 <sup>b</sup>	<b>1a</b>	0.2	0.04	18	19	90	44 ( <i>S</i> )
3 <sup>c</sup>	<b>1a</b>	0.2	0.04	18	43	76	4 ( <i>R</i> )
4	<b>1a</b>	0.1	0.03	18	19	77	38 ( <i>S</i> )
5	<b>1a</b>	0.2	0.04	18	19	85	74 ( <i>S</i> )
6	<b>1a</b>	0.4	0.05	18	19	85	82 ( <i>S</i> )
7	<b>1a</b>	0.4	0.1	18	4	91	81 ( <i>S</i> )
8	<b>1a</b>	0.4	0.1	-23	140	75	53 ( <i>S</i> )
9	<b>1a</b>	0.6	0.06	18	19	95	81 ( <i>S</i> )
10	<b>1a</b>	0.6	0.04	18	19	90	78 ( <i>S</i> )
11	<b>1a</b>	0.8	0.07	18	43	74	73 ( <i>S</i> )
12	<b>1a</b>	1.0	0.08	18	43	23	66 ( <i>S</i> )

<sup>a</sup> Reaction in the absence of  $\text{Ti}(\text{O}^i\text{Pr})_4$ .

<sup>b</sup> Addition order was reversed from  $\text{Ti}(\text{O}^i\text{Pr})_4/\text{Et}_3\text{Al}$  to  $\text{Et}_3\text{Al}/\text{Ti}(\text{O}^i\text{Pr})_4$ .

<sup>c</sup> Reaction in the presence of  $\text{Ti}(\text{O}^i\text{Bu})_4$  instead of  $\text{Ti}(\text{O}^i\text{Pr})_4$ .

proceeds with low asymmetric induction yielding (*R*) product (Table 2, entry 1). Addition of aluminum and titanium reagents in the reversed order influenced the enantioselectivity greatly (Table 2, entries 2 and 3), which suggests a transition state different from the one proposed for the analogous diethylzinc addition.<sup>1</sup> The reaction is even more susceptible to bulkiness of the titanium reagent. In the presence of Ti(O<sup>*i*</sup>Bu)<sub>4</sub> the *R* enantiomer was obtained in 4% ee and accompanied by 27.6% of benzyl alcohol (Table 2, entry 4).<sup>5</sup> The optimal amount of ligand **1a** was found to be 0.4 equiv at the concentration 0.1 mmol/mL at room temperature (Table 2, entries 5–13).

**2.1.2. Enantioselective triethylaluminum addition to aldehydes in the presence of various  $\alpha$ -hydroxy acids.** After the best conditions had been established for the ligand **1a**, we performed a series of reactions in the presence of ligands **1b–h** (Table 3). The best result, 90% ee, was obtained for ligand **1b**.

As already mentioned, the main products were accompanied by benzyl alcohol **4**. The amount of **4** was dependent on the reaction conditions, ligand type, and amount. Fortunately, in the presence of 0.4 equiv of

**Table 3.** Addition reactions of Et<sub>3</sub>Al to benzaldehyde in the presence of ligands **1a–h**


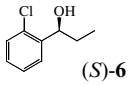
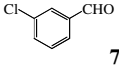
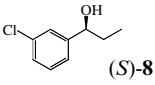
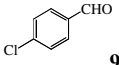
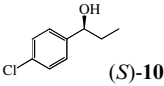

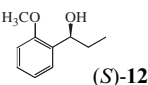
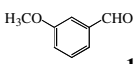
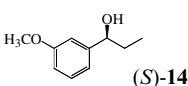
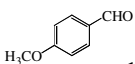
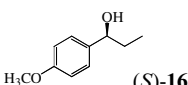
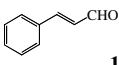
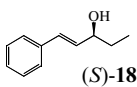
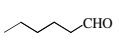
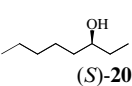
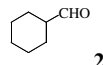
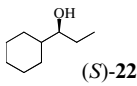
Entry	Ligand	Amount [equiv]	Temp [°C]	Time [h]	Yield [%]	Ee (config.) [%]
1	<b>1a</b>	0.4	18	4	91	81 ( <i>S</i> )
2	<b>1b</b>	0.4	18	4	96	90 ( <i>S</i> )
3	<b>1c</b>	0.4	18	4	95	87 ( <i>S</i> )
4	<b>1d</b>	0.4	18	4	96	88 ( <i>S</i> )
5	<b>1e</b>	0.4	18	19	88	80 ( <i>S</i> )
6	<b>1f</b>	0.4	19	19	95	81 ( <i>S</i> )
8	<b>1g</b>	0.4	19	4	95	84 ( <i>S</i> )
9	<b>1h</b>	0.4	19	4	95	82 ( <i>S</i> )

ligand **1b** the amount of benzyl alcohol increased only slightly when compared to ligand **1a** (Table 4, entry 4

**Table 4.** Amount of benzyl alcohol in reaction mixture

Entry	Ligand	Ligand amount [equiv]	Concn [mmol/mL]	Time [h]	Ratio <b>4:3a</b>	Amount of <b>4</b> [%]
1	<b>1a</b>	0.2	0.04	19	1:14	7.5
2	<b>1a</b>	0.4	0.05	19	1:57	1.2
3	<b>1a</b>	0.4	0.1	4	1:125	0.8
4	<b>1b</b>	0.4	0.1	4	1:72	1.4

**Table 5.** Addition reactions of Et<sub>3</sub>Al to benzaldehyde in the presence of ligand **1b**

Entry	Aldehyde	Temp [°C]	Time [h]	Product	Yield [%]	Ee [%]
1	 <b>5</b>	20	4	 ( <i>S</i> )- <b>6</b>	92	85
2	 <b>7</b>	20	6	 ( <i>S</i> )- <b>8</b>	95	79
3	 <b>9</b>	21	4	 ( <i>S</i> )- <b>10</b>	85	89
4	 <b>11</b>	21	4	 ( <i>S</i> )- <b>12</b>	85	89
5	 <b>13</b>	20	4	 ( <i>S</i> )- <b>14</b>	95	92
6	 <b>15</b>	20	6	 ( <i>S</i> )- <b>16</b>	90	66
7	 <b>17</b>	21	4	 ( <i>S</i> )- <b>18</b>	80	63
8	 <b>19</b>	21	4	 ( <i>S</i> )- <b>20</b>	70	77
9	 <b>21</b>	21	4	 ( <i>S</i> )- <b>22</b>	82	83

vs 1–3), while the enantiomeric excess was higher than for other ligands.

The enantioselective addition of triethylaluminum to some representative aromatic and aliphatic aldehydes was performed in the presence of 0.4 equiv of ligand **1b**. The resulting ee was highly dependent on the structure of the aldehyde. It is worth stressing that reasonably good enantioselectivities were obtained for aliphatic and cycloaliphatic aldehydes (Table 5).

## 2.2. Enantioselective trimethylaluminum addition

Finally, we performed the addition of another organoaluminum reagent—trimethylaluminum. We chose ligands **1b** and **1d**, which had given high ee for trimethylaluminum additions to benzaldehyde. The reactions proceeded with very good yield, but the enantioselectivity was lower than that obtained for Et<sub>3</sub>Al (Table 6).

## 2.3. Mechanistic considerations

The stereochemical outcome of the reaction performed in the presence of  $\alpha$ -hydroxy carboxylic acids can be rationalized as follows: The reaction is highly dependent on the order of addition of titanium and aluminum reagents. This suggests two different transition states, and also, that transition state in the case of organoaluminum reagents differs from that observed for organozinc compounds. We suppose that in this case reaction proceeds through a bimetallic transition state similar to that already proposed by Seebach et al. (Fig. 1).<sup>6</sup>

The  $\alpha$ -hydroxy carboxylic acid makes an aggregate with two titanium compounds, one of them being a coordination center for ligand and aldehyde, the second carries an ethyl group transferred from Et<sub>3</sub>Al. The key factor for good asymmetric induction is the presence of hydrogen bonding between the ligand's  $\alpha$ -oxygen and the

hydrogen of the coordinated aldehyde. Such bonding was already postulated by Corey and Lee,<sup>7</sup> and was proved to be a very important factor influencing asymmetric induction in enantioselective reactions, also in the reactions catalyzed by  $\alpha$ -hydroxy acids.<sup>1</sup> Its presence substantially rigidifies transition states leading to good enantiomeric excesses. The proposed model also explains the influence of the bulky substituents on titanium tetraalkoxide on the enantioselectivity. The increased steric clash of alkyl groups connected to the oxygen bridge results in a weaker hydrogen bond and, probably a seriously reorganized transition state.

## 3. Conclusions

We have shown that the addition reactions to the carbonyl group of aldehydes in the presence of  $\alpha$ -hydroxy carboxylic acids proceed with very good yields and good enantiomeric excesses up to 92%.  $\alpha$ -Hydroxy acids can catalyze the addition of trialkylaluminum to both aliphatic and aromatic aldehydes, which are relatively inexpensive and readily available. Further applications of  $\alpha$ -hydroxy acids as ligands for enantioselective organometallic additions are under investigation and will be reported in due course.

## 4. Experimental

### 4.1. General

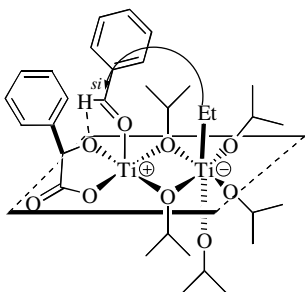
Melting points were determined using a Kofler hot stage apparatus and are uncorrected. Specific rotations were recorded using a Perkin–Elmer PE-241 polarimeter with a thermally jacketed 10-cm cell. Reactions were carried under argon using Schlenk technique when necessary. Flash column chromatography was made on silica gel (Kieselgel-60, Merck, 230–400 mesh). High performance liquid chromatography was conducted on Merck Hitachi D-7000 with diode array detector L-7455 using chiral column Diacel Chiracel OD. Gas chromatography was conducted on Hewlett Packard 5890 series II with FID detector using chiral column  $\beta$ -Dex, 30 m  $\times$  0.25 mm I.D. (Supelco, Bellefonte, USA). Retention time is given in minutes.  $\alpha$ -Hydroxy carboxylic acids were obtained according to published procedures.

### 4.2. General procedure for the addition of triethyl- and trimethylaluminum to aldehyde in the presence (*S*)-mandelic acid

In the oven dried Schlenk tube filled with argon and equipped with the stirring bar was placed (*S*)-mandelic acid (30.2 mg, 0.2 mmol), followed by THF (2 mL), Ti(O<sup>*i*</sup>Pr)<sub>4</sub> (0.42 mL, 1.4 mmol). After 1 h the solution was cooled to 0 °C and triethylaluminum (1.9 M in toluene, 0.8 mL, 1.5 mmol) was added. The stirring was continued at this temperature for 30 min, aldehyde (1 mmol) was added and after additional 30 min of stirring at 0 °C the reaction mixture was allowed to warm up to room temperature. The progress of the reaction was monitored with TLC using CH<sub>2</sub>Cl<sub>2</sub>/MeOH 70:2.

**Table 6.** Addition reactions of Me<sub>3</sub>Al to benzaldehyde in the presence of ligands **1b** and **1d**

Ligand	Amount [equiv]	Temp [°C]	Time [h]	Yield [%]	Ee [%]
<b>1b</b>	0.4	22	2.5	95	80 ( <i>S</i> )
<b>1d</b>	0.4	22	2.5	95	78 ( <i>S</i> )



**Figure 1.**

After completion the reaction was quenched with slow addition of 1 M HCl (10 mL) (CAUTION! Exothermic reaction). The precipitate was filtered off using funnel with cotton plug and the filtrate was extracted three times with ethyl acetate (3 × 20 mL), combined extracts were washed with brine (30 mL), dried over anhydrous MgSO<sub>4</sub>, and evaporated in vacuo. The resulting oil was purified by flash chromatography (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 200:3 as eluent). All compounds have been previously reported and were characterized by comparison with their reported physical and spectroscopic data.

**4.2.1. (S)-1-Phenyl-1-propanol (S)-3.** HPLC:  $t_S = 12.1$ ,  $t_R = 13.2$  (hexane/<sup>i</sup>PrOH 97:3, flow 1 mL/min);  $[\alpha]_D^{20} = -42.0$  ( $c$  1.0, CHCl<sub>3</sub>); ee = 90.4%, lit.<sup>8</sup>  $[\alpha]_D^{20} = -44.4$  ( $c$  1.01, CHCl<sub>3</sub>), ee = 95.5%.

**4.2.2. (S)-1-(2-Chlorophenyl)-1-propanol (S)-18.** GC:  $t_R = 51.0$ ,  $t_S = 54.2$  ( $T_{\text{column}} = 130$  °C,  $P = 100$  kPa),  $[\alpha]_D^{20} = -48.6$  ( $c$  1.25, benzene), ee = 85%.

**4.2.3. (S)-1-(3-Chlorophenyl)-1-propanol (S)-19.** HPLC:  $t_S = 17.1$ ,  $t_R = 18.6$  (hexane/<sup>i</sup>PrOH 96:4, flow 0.5 mL/min);  $[\alpha]_D^{20} = -23.3$  ( $c$  1.21, benzene), ee = 78.8%, lit.<sup>9</sup>  $[\alpha]_D^{20} = +26.6$  ( $c$  2.36, benzene) for the (*R*)-enantiomer, ee = 97%.

**4.2.4. (S)-1-(4-Chlorophenyl)-1-propanol (S)-20.** HPLC:  $t_S = 22.4$ ,  $t_R = 24.3$  (hexane/<sup>i</sup>PrOH 97:3, flow 0.5 mL/min);  $[\alpha]_D^{20} = -23.6$  ( $c$  1.77, benzene), ee = 88.5%, lit.<sup>8</sup>  $[\alpha]_D^{20} = -23.6$  ( $c$  1.73, benzene), ee = 93%.

**4.2.5. (S)-1-(2-Methoxyphenyl)-1-propanol (S)-21.** HPLC:  $t_S = 27.5$ ,  $t_R = 29.6$  (hexane/<sup>i</sup>PrOH 97:3, flow 0.5 mL/min);  $[\alpha]_D^{20} = -50.8$  ( $c$  1.22, toluene), ee = 89.1%, lit.<sup>8</sup>  $[\alpha]_D^{22} = -52.9$  ( $c$  1.02, toluene), ee = 91%.

**4.2.6. (S)-1-(3-Methoxyphenyl)-1-propanol (S)-22.** HPLC:  $t_S = 80.3$ ,  $t_R = 76.6$  (hexane/<sup>i</sup>PrOH 97:3, flow 0.3 mL/min);  $[\alpha]_D^{20} = -26.8$  ( $c$  0.8, toluene), ee = 92%.

**4.2.7. (S)-1-(4-Methoxyphenyl)-1-propanol (S)-23.** HPLC:  $t_S = 38.1$ ,  $t_R = 33.6$  (hexane/<sup>i</sup>PrOH 97:3, flow 0.5 mL/min);  $[\alpha]_D^{20} = -28.7$  ( $c$  1, benzene), ee = 83%, lit.<sup>8</sup>  $[\alpha]_D^{20} = -25.8$  ( $c$  1.1, benzene), ee = 74%.

**4.2.8. (S)-1-Phenyl-1-penten-3-ol (S)-24.** HPLC:  $t_S = 13.0$ ,  $t_R = 9.0$  (hexane/<sup>i</sup>PrOH 90:10, flow 1.0 mL/min);

$[\alpha]_D^{20} = -4.9$  ( $c$  1, CHCl<sub>3</sub>), ee = 63%. lit.<sup>10</sup>  $[\alpha]_D^{20} = -6.3$  ( $c$  1.73, CHCl<sub>3</sub>), ee = 59%.

**4.2.9. (S)-3-Octanol (S)-25.** HPLC (as benzoate):  $t_S = 21.1$ ,  $t_R = 23.1$  (hexane, flow 0.5 mL/min),  $[\alpha]_D^{20} = +7.6$  ( $c$  1.03, CHCl<sub>3</sub>); ee = 77%, lit.<sup>8</sup>  $[\alpha]_D^{20} = +5.87$  ( $c$  1, CHCl<sub>3</sub>), ee = 60%.

**4.2.10. (S)-1-Cyclohexyl-1-propanol (S)-26.** HPLC (as benzoate):  $t_S = 37.8$ ,  $t_R = 35.9$  (hexane/<sup>i</sup>PrOH 99.9:0.1, flow 0.2 mL/min);  $[\alpha]_D^{20} = -5.4$  ( $c$  1.14, CHCl<sub>3</sub>), ee = 82.5%, lit.<sup>8</sup>  $[\alpha]_D^{24} = -6.39$  ( $c$  1.05, CHCl<sub>3</sub>), ee = 97%.

**4.2.11. (S)-1-Phenyl-1-ethanol.** HPLC:  $t_S = 14.8$ ,  $t_R = 12.8$  (hexane/<sup>i</sup>PrOH 97:3, flow 1 mL/min);  $[\alpha]_D^{20} = -43.9$  ( $c$  1.38, CHCl<sub>3</sub>); ee = 79.5%, lit.<sup>11</sup>  $[\alpha]_D^{20} = -66.5$  ( $c$  0.6, CHCl<sub>3</sub>) ee = 98%.

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