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## Full Papers

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### Catalytic enantioselective alkylation of aldehydes using chiral hydrogen phosphoramidates and hydrogen phosphinamides and their thio analogs

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(Received October 20, 1994)

**Abstract.** Chiral (enantiomerically pure) hydrogen thiophosphoramidates and hydrogen phosphoramidates and their phosphinamide analogs derived from norephedrine and other chiral (enantiomerically pure) amino alcohols catalyze the enantioselective addition of dialkylzinc to aldehydes. The presence of titanium tetraisopropoxide increases the enantioselectivity, providing enantiomerically enriched secondary alcohols with up to 98% *ee*. The enantioselectivities of thiophosphoramidates and thiophosphinamides are higher than those of the oxygen analogs. The phosphoramidates and thiophosphoramidates, without the hydroxyl group, also catalyze the addition of dialkylzinc to aldehydes in the absence of  $\text{Ti}(\text{O}^i\text{Pr})_4$ .

#### Introduction

Enantioselective additions of organozinc reagents to aldehydes have attracted much attention<sup>1</sup>. The rate of this reaction in case of dialkylzinc without catalyst is very low. It is known that dialkylzinc requires an additive such as magnesium halide to add to aldehydes in reasonable yields<sup>2</sup>. Mukaiyama et al. reported the addition of diethylzinc to benzaldehyde in the presence of an amino alcohol derived from (*S*)-proline<sup>3</sup>. Catalytic enantioselective additions of dialkylzinc to aldehydes using chiral (enantiomerically pure) amino alcohols have also been reported<sup>4</sup>. We have reported the highly enantioselective addition of organozinc reagents to aldehydes using chiral (enantiomerically pure) amino alcohols<sup>5</sup>, piperazines<sup>6</sup>, ammonium salts<sup>7</sup>, and polymer-supported amino alcohols<sup>8</sup>. Other chiral (enantiomerically pure) catalysts utilized in the reaction involve, for example, 1,2-diols<sup>9</sup>, pyridinamines<sup>10</sup>, thiol derivatives<sup>11</sup> and pyridinol<sup>12</sup>. We also reported the chiral automultiplication reaction using chiral (enantiomerically enriched) pyridinol<sup>13</sup> and chiral (enantiomerically enriched) diol<sup>14</sup> as asymmetric autocatalysts<sup>15</sup>. Recently, the enantioselective addition of dialkylzinc to aldehydes using chiral (enantiomerically pure) sulfonamides<sup>16</sup> and diols<sup>17</sup> in the presence of titanium tetraisopropoxide [ $\text{Ti}(\text{O}^i\text{Pr})_4$ ] was reported.

We recently reported the enantioselective addition of dialkylzinc to phosphinylimines [ $\text{R}_2\text{P}(\text{O})\text{N}=\text{CHR}'$ ] in the presence of chiral (enantiomerically pure) amino alcohols. Enantiomerically enriched phosphinamides [ $\text{R}_2\text{P}(\text{O})\text{NCHR}''$ ] with high *ees*<sup>a</sup> are subsequently obtained which, after acidic hydrolysis, afford enantiomerically enriched amines also in high *ees*<sup>18</sup>. Although dialkyl thiophosphoramidate [ $(\text{RO})_2\text{P}(\text{S})\text{NR}'_2$ ]<sup>19</sup>

and dialkylthiophosphinamide<sup>20</sup> are known as protecting groups of amines, enantiomerically pure phosphoramidates and phosphinamides and their thio analogs have rarely been utilized as chiral catalysts and chiral ligands for enantioselective synthesis<sup>21</sup>.

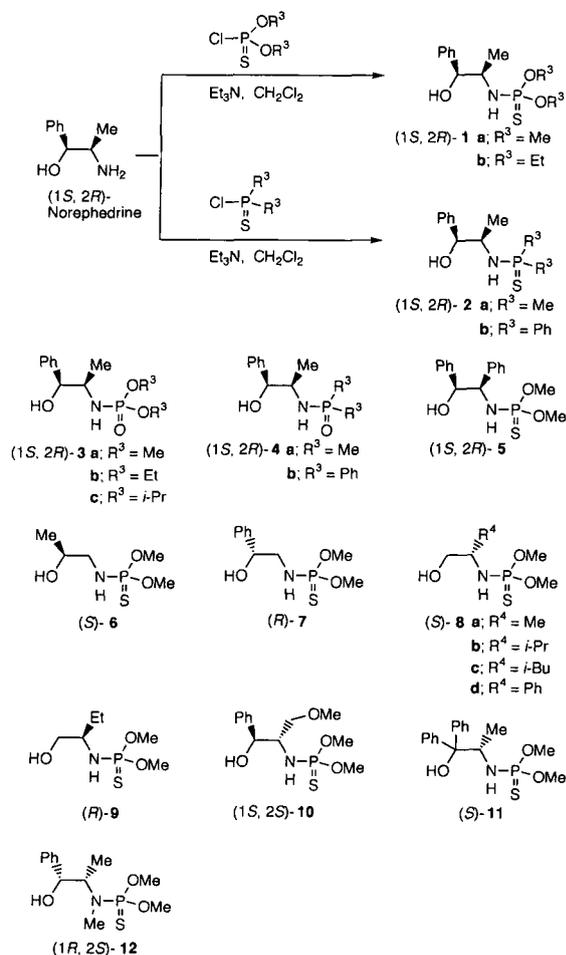
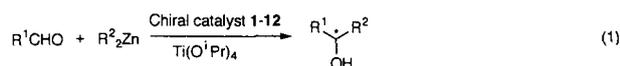
Here, we report the enantioselective addition of dialkylzinc to aldehydes using enantiomerically pure thiophosphoramidates, phosphoramidates, thiophosphinamides and phosphinamides as chiral catalysts in the presence of titanium tetraisopropoxide (Eqn. 1)<sup>22</sup>.

#### Results and discussions

The syntheses of the chiral catalysts are summarized in Scheme 1. (*1S,2R*)-*N*-(*O,O*-dialkylthiophosphoryl)norephedrines<sup>b</sup> **1a,b** were prepared in 62 and 79% yields, respectively, from (*1S,2R*)-norephedrine and the corresponding dialkyl chlorothiophosphates in the presence of triethylamine (the by-product which was thiophosphorylated at the OH was not formed at  $-30^\circ\text{C}$ ). (*1S,2R*)-*N*-(Dimethylthiophosphinyl)- and -*N*-(diphenylthiophosphinyl)norephedrines **2a,b** were synthesized from norephedrine and dimethyl- and diphenylthiophosphinyl chloride, respectively. (*1S,2R*)-*N*-(*O,O*-Dialkylphosphoryl)norephedrines **3a-c** were prepared in a similar manner to **1a,b** using the corresponding dialkyl chlorophosphates instead of the dialkyl chlorothiophosphates. (*1S,2R*)-*N*-(dimethylphosphinyl)- and -*N*-(diphenylphosphinyl)norephedrines **4a,b** were synthesized from dimethyl- and diphenylphosphinyl chloride, respectively. (*1S,2R*)-2-[(*O,O*-dimethylthiophosphoryl)amino]-1,2-diphenylethanol **5** was prepared from (*1S,2R*)-2-amino-1,2-diphenylethanol<sup>23</sup> using

<sup>a</sup> *ee* = enantiomeric excess

<sup>b</sup> Norephedrine = 2-amino-1-phenylpropan-1-ol = (*Chem. Abstr.* name)  $\alpha$ -(1-aminoethyl)benzenemethanol.



Scheme 1. Synthesis of chiral catalysts

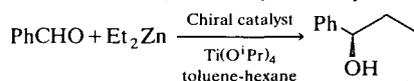
dimethyl chlorothiophosphate. Catalysts 6–11 were prepared from the corresponding amino alcohols. Catalyst 12, in which the nitrogen atom has a methyl group instead of a hydrogen atom, was derived from (1*R*,2*S*)-ephedrine<sup>c</sup>.

We first examined the effect of the phosphoryl [(RO)<sub>2</sub>P(O)-] and phosphinyl [R<sub>2</sub>P(O)-] substituents on the nitrogen atom of the norephedrine-derived chiral catalysts (5 mol%) during the enantioselective addition of diethylzinc (1.5 eq.) to benzaldehyde (1 eq.) in the presence of titanium tetraisopropoxide (1.5 eq.). The results are shown in Table I. The following conclusions can be drawn from the data in Table I. In all cases, diethylzinc attacks from the *si* face of benzaldehyde to afford (*S*)-1-phenylpropan-1-ol<sup>d</sup>. A dramatic difference was observed between the behaviors of P=S and P=O groups. Both the synthetic yield and the *ee* of the obtained 1-phenylpropan-1-ol are higher, using sulfur-containing chiral catalysts than using the corresponding oxygen-containing chiral catalysts (entries 2 and 3; 4 and 5; 6 and 7). The dimethylthiophosphinyl group [Me<sub>2</sub>P(S)-] affords a higher *ee* (74% *ee*) than the diphenylthiophosphinyl group [Ph<sub>2</sub>P(S)-] (64% *ee*) (entries 4 and 6). When dimethyl-(1*a*) and diethylthiophosphoryl (1*b*) groups are compared,

<sup>c</sup> Ephedrine = 2-(methylamino)-1-phenylpropan-1-ol = (*Chem. Abstr. name*) α-[1-(methylamino)ethyl]benzenemethanol.

<sup>d</sup> *Chem. Abstr. name*: α-ethylbenzenemethanol.

Table I The effect of the structure of chiral catalysts derived from norephedrine and ephedrine on the enantioselective addition of diethylzinc to benzaldehyde in the presence of titanium tetraisopropoxide.



Entry <sup>a</sup>	Chiral catalyst	Temp. (°C)	Time (h)	(S)-1-Phenylpropan-1-ol	
				Yield (%)	<i>ee</i> (%) <sup>b</sup>
1	<b>1a</b>	-35 to -20	1.3	98	93
2	<b>1b</b>	-35 to -20	1.3	97	88
3	<b>3b</b>	-40 to -10	2.5	89	49
4	<b>2a</b>	-35 to -20	3.0	98	74
5	<b>4a</b>	-35 to -10	4.0	88	25
6	<b>2b</b>	-35 to -15	3.0	94	64
7	<b>4b</b>	-50 to -10	5.0	88	40
8 <sup>c</sup>	<b>12</b>	-40 to 0	5.0	28	1

<sup>a</sup> Unless otherwise noted, the molar ratio was PhCHO/Et<sub>2</sub>Zn/chiral-catalyst/Ti(O<sup>*i*</sup>Pr)<sub>4</sub> = 1/1.5/0.05/1.5. A mixed solvent of toluene and hexane was used. <sup>b</sup> Determined by HPLC analysis using a chiral column. Daicel Chiralcel OB; 4 × 250 mm, 254 nm UV detector, room temperature, eluent: 3% propan-2-ol in hexane, flow rate: 0.5 ml/min, retention time (min), 19 for major (*S*)-isomer, 26 for minor (*R*)-isomer. <sup>c</sup> Molar ratio was PhCHO/Et<sub>2</sub>Zn/12/Ti(O<sup>*i*</sup>Pr)<sub>4</sub> = 1/1.5/0.15/0.8.

similar enantioselectivities (88 and 93% *ee*) were observed (entries 1 and 2). The *O,O*-dimethylthiophosphoryl group (1*a*) is more enantioselective (93% *ee*) than the *O,O*-dimethylthiophosphinyl group (2*a*), (74% *ee*, entries 1 and 4). On the other hand, when (1*R*,2*S*)-12 (with a methyl substituent on the nitrogen atom instead of a hydrogen atom) was employed, both the yield and the *ee* of the obtained alcohol dropped dramatically (entry 8). Thus (1*S*,2*R*)-1*a*, in which the dimethylthiophosphoryl group and the hydrogen atom on the nitrogen atom are present, was found to be a highly enantioselective chiral catalyst. We then examined the effect of the structure of the enantiomerically pure *O,O*-dimethylthiophosphoryl catalysts derived from various optically pure amino alcohols. The results are summarized in Table II. Chiral catalyst (1*S*,2*R*)-5 (possessing a phenyl substituent instead of the methyl substituent of catalyst 1*a*) is a promising candidate to afford (*S*)-1-phenylpropan-1-ol with a 84% *ee* (entry 1). Chiral catalysts (1*S*,2*R*)-1–4 derived from norephedrine (Table I) and (1*S*,2*R*)-5 (Table II, entry 1) have two stereogenic centers and are (*S*)-selective. In order to clarify whether two stereogenic centers are necessary, we examined the reaction using chiral catalysts possessing one stereogenic center. Chiral catalysts (*S*)-6 and (*R*)-7 (possessing a stereogenic center at the alcohol moiety) afforded 1-phenylpropan-1-ol with 21% *ee* (*S*) and 38% *ee* (*R*), respectively (entries 2 and 3). Catalyst 7 (with the phenyl substituent) is more enantioselective than the catalyst 6 (with the methyl substituent). On the other hand,

Table II The effect of the structure of chiral catalysts derived from the corresponding enantiomerically pure aminoalcohols.

Entry <sup>a</sup>	Chiral catalyst	Et <sub>2</sub> Zn (eq.)	Temp. (°C)	Time (h)	(S)-1-Phenylpropan-1-ol	
					Yield (%)	<i>ee</i> (%) <sup>b</sup>
1	<b>5</b>	1.5	-30-0	5	41	84 ( <i>S</i> )
2	<b>6</b>	1.5	-30-0	5	9	21 ( <i>S</i> )
3	<b>7</b>	1.5	-30-0	5	36	38 ( <i>R</i> )
4	<b>8a</b>	3	-30	7	23	37 ( <i>R</i> )
5	<b>8b</b>	3	-30	7	27	24 ( <i>R</i> )
6	<b>8c</b>	3	-30	7	31	50 ( <i>R</i> )
7	<b>8d</b>	1.5	-30-0	5	24	53 ( <i>R</i> )
8	<b>9</b>	3	-30	7	52	32 ( <i>S</i> )
9	<b>11</b>	1.5	-30-0	5	17	18 ( <i>S</i> )
10	<b>10</b>	3	-30	7	29	33 ( <i>S</i> )

<sup>a</sup> PhCHO/Et<sub>2</sub>Zn/chiral-catalyst/Ti(O<sup>*i*</sup>Pr)<sub>4</sub> = 1/(1.5–3)/0.15/0.8. A mixed solvent of toluene and hexane was used. <sup>b</sup> See footnote b in Table I.

Table III The effect of the molar ratio of the reagents on the enantioselective addition of diethylzinc to benzaldehyde using chiral catalysts in the presence of titanium tetraisopropoxide.

Entry <sup>a</sup>	Et <sub>2</sub> Zn (eq.)	Catalyst (eq.)	Ti(O <sup>i</sup> Pr) <sub>4</sub> (eq.)	(S)-1-Phenylpropan-1-ol	
				Yield (%)	ee (%) <sup>b</sup>
1	3.0	<b>1a</b> (0.15)	0.4	33	93
2	3.0	<b>1a</b> (0.15)	0.8	80	96
3	3.0	<b>1a</b> (0.15)	1.2	90	96
4	3.0	<b>1a</b> (0.15)	1.6	83	96
5	3.0	<b>1a</b> (0.05)	1.2	88	94
6	3.0	<b>1a</b> (0.15)	1.2	90	95
7	3.0	<b>1a</b> (0.25)	1.2	93	96
8	3.0	<b>1a</b> (0.50)	1.2	88	96
9	1.0	<b>1a</b> (0.15)	1.2	47	95
10	2.0	<b>1a</b> (0.15)	1.2	92	95
11	3.0	<b>1a</b> (0.15)	1.2	90	96
12	4.0	<b>1a</b> (0.15)	1.2	93	96
13 <sup>c</sup>	2.0	<b>1a</b> (0.05)	none	88	54
14	1.5	<b>3b</b> (0.05)	1.5	89	49
15	3.0	<b>3b</b> (0.15)	1.2	85	85
16	3.0	<b>3a</b> (0.15)	1.2	43	65
17	3.0	<b>3c</b> (0.15)	1.2	81	84

<sup>a</sup> The reactions were run in a mixed solvent of toluene and hexane at  $-30^{\circ}\text{C}$  for 5 h. <sup>b</sup> See footnote b in Table I. <sup>c</sup> The reaction was run at room temperature.

among the chiral catalysts (*S*)-**8a-d**, (*R*)-**9** and (*S*)-**11** (with a stereogenic center bonded to the nitrogen atom; entries 4–9), **8c** and **8d** (with relatively bulky isobutyl and phenyl substituents) afforded (*R*)-1-phenylpropan-1-ol with moderate *ees* (entries 6 and 7). (*1S,2S*)-**10** gave (*S*)-1-phenylpropan-1-ol with a low *ee* (entry 10). Chiral catalyst **1a** has the same (phenyl and methyl) substituents as both **7** (phenyl) and **8a** (methyl), although the configurations are opposite. Based on the results that both chiral catalysts (*R*)-**7** and (*S*)-**8a** have the same direction of enantioselectivity affording (*R*)-1-phenylpropan-1-ol (Table II, entries 3 and 4), both of the stereogenic centers of (*1S,2R*)-**1a** should be (*S*)-selective. Thus, chiral (*1S,2R*) catalysts (with two stereogenic centers **1a**, **b** and **5**) are more enantioselective than those with one stereogenic center.

On the other hand, the enantioselectivity of (*S*)-**11** (with two phenyl substituents on the alcohol moiety) is opposite that of (*S*)-**8a**.

The effect of the molar ratio of the reagents was examined for the enantioselective addition of diethylzinc to benzaldehyde using **1a** and **3a-c** as chiral catalysts in the presence of Ti(O<sup>i</sup>Pr)<sub>4</sub>. The results are summarized in Table III. As to the effect of Ti(O<sup>i</sup>Pr)<sub>4</sub>, the *ees* of 1-phenylpropan-1-ol are high (93–96% *ee*) regardless of the amount of Ti(O<sup>i</sup>Pr)<sub>4</sub> (0.4–1.6 eq.) (entries 1–4). With regard to the synthetic yield, the use of 1.2 eq. of Ti(O<sup>i</sup>Pr)<sub>4</sub> is enough to achieve a high yield (entry 3). Thus Ti(O<sup>i</sup>Pr)<sub>4</sub> plays an activating role. The effect of the amount of the chiral catalyst **1a** (0.05 to 0.5 eq.) was examined (entries 5–8). Both yields (88–93%) and *ees* (94–96% *ee*) were almost constant regardless of the amount of **1a**. The amount of Et<sub>2</sub>Zn did affect the yield of 1-phenylpropan-1-ol (entries 9–12), although the *ees* were almost constant. The use of excess Et<sub>2</sub>Zn affords 1-phenylpropan-1-ol with high 95–96% *ees* in high yields (90–93%) (entries 10–12).

On the other hand, **1a** (0.05 eq.) catalyzes the addition reaction even without Ti(O<sup>i</sup>Pr)<sub>4</sub> at room temperature to afford 1-phenylpropan-1-ol in 88% yield but with moderate *ee* (entry 13).

In addition, the use of 15 mol% *O,O*-dialkylphosphoryl chiral catalysts **3b**, **c** and 3 eq. of Et<sub>2</sub>Zn dramatically increased the enantioselectivity [from 49% *ee* (entry 14; also Table I, entry 3) to up to 84–85% *ee* (Table III, entries 15 and 17)]. Among the *O,O*-dialkylphosphoryl

Table IV. The effect of the solvent on the enantioselective addition of diethylzinc to benzaldehyde using **1a** in the presence of titanium tetraisopropoxide.

Entry <sup>a</sup>	Solvent	(v/v)	(S)-1-Phenylpropan-1-ol	
			Yield (%)	ee (%) <sup>b</sup>
1	Hexane		79	95
2	Toluene		87	96
3	Hexane-Toluene	3/2	90	96
4	THF-Hexane	2/3	70	93
5	Et <sub>2</sub> O-Hexane	2/3	88	94
6	CH <sub>2</sub> Cl <sub>2</sub> -Hexane	2/3	86	98
7	CH <sub>3</sub> CN-Hexane	2/3	91	95
8	THF-Toluene	2/3	70	94
9	Et <sub>2</sub> O-Toluene	2/3	91	96
10	CH <sub>2</sub> Cl <sub>2</sub> -Toluene	2/3	90	97
11	CH <sub>3</sub> CN-Toluene	2/3	90	98
12 <sup>c</sup>	Benzene-Hexane	2/3	93	96
13	Benzene-Toluene	2/3	88	96

<sup>a</sup> PhCHO/Et<sub>2</sub>Zn/**1a**/Ti(O<sup>i</sup>Pr)<sub>4</sub> = 1/3/0.15/1.2. Unless otherwise noted, the reaction temperature was  $-30^{\circ}\text{C}$ . <sup>b</sup> See footnote b in Table I. <sup>c</sup> The reaction temperature was  $-20^{\circ}\text{C}$ .

chiral catalysts (**3a-c**), catalysts **3b,c** with large ethoxy and isopropoxy substituents are more enantioselective than the small methoxy substituent in **3a** (entry 16).

The effect of the solvent during the enantioselective addition of diethylzinc to benzaldehyde [using **1a** as a chiral catalyst in the presence of Ti(O<sup>i</sup>Pr)<sub>4</sub> at  $-30^{\circ}\text{C}$ ] is shown in Table IV. It should be noted that a variety of solvents, *i.e.*, hexane, toluene, benzene, THF, diethyl ether, dichloromethane and acetonitrile, afforded 1-phenylpropan-1-ol with high (94–98%) *ees* in good to high yields. The relatively mild reactivity of dialkylzinc made it possible to use diethyl ether, dichloromethane and acetonitrile. These solvents cannot be usually used with highly nucleophilic alkyllithium and Grignard reagents.

The effect of temperature is shown in Table V. The *ees* of 1-phenylpropan-1-ol are high when the reaction temperatures were between  $-60$  to  $0^{\circ}\text{C}$  (entries 1–3). The *ee* slightly decreased when the reaction was run at room temperature ( $25^{\circ}\text{C}$ ) (entry 4).

With regard to the effect of metal alkoxides, Ti(O<sup>i</sup>Pr)<sub>4</sub> was found to be the most efficient. During the ethylation of benzaldehyde using (*1S,2R*)-**1a** (15 mol%), in which Ti(O<sup>i</sup>Pr)<sub>4</sub> affords (*S*)-1-phenylpropan-1-ol with 95% *ee*, aluminum(III) and zirconium(IV) isopropoxides (0.8 eq.) afforded (*S*)-alcohol with only 18 and 7% *ee*, respectively. Ti(OEt)<sub>4</sub> was *S*-enantioselective (*S*: 72% *ee*) and Ti(O<sup>i</sup>Bu)<sub>4</sub> provided the (*S*)-alcohol with 54% *ee*. Interestingly, the enantioselectivity of boron(III) isopropoxide was the opposite (*R*: 26% *ee*).

The enantioselective addition of dialkylzincs to various aldehydes using chiral catalyst (*1S,2R*)-**1a** in the presence of Ti(O<sup>i</sup>Pr)<sub>4</sub> is summarized in Table VI. Dimethylzinc afforded (*S*)-1-phenylethan-1-ol with 97% *ee* in 78% yield (Table VI, entry 1). The reaction rate of the present method ( $-30^{\circ}\text{C}$ , 2 h) is faster than that using the enantiomerically pure amino alcohol catalyst<sup>5b,c</sup>. The enantio-

Table V The effect of temperature on the enantioselective addition of diethylzinc to benzaldehyde using chiral catalyst **1a** in the presence of titanium tetraisopropoxide.

Entry <sup>a</sup>	Temperature (°C)	Time (h)	(S)-1-Phenylpropan-1-ol	
			Yield (%)	ee (%) <sup>b</sup>
1	$-60$	6	83	96
2	$-30$	5	90	96
3	0	1.3	92	93
4	25	1.3	86	83

<sup>a</sup> PhCHO/Et<sub>2</sub>Zn/**1a**/Ti(O<sup>i</sup>Pr)<sub>4</sub> = 1/3/0.15/1.2. A mixed solvent (hexane and toluene) was used. <sup>b</sup> See footnote b in Table I.

Table VI Enantioselective addition of dialkylzincs to various aldehydes using chiral catalyst **1a** in the presence of  $\text{Ti}(\text{O}^i\text{Pr})_4$ .

$$\text{R}^1\text{CHO} + \text{R}^2_2\text{Zn} \xrightarrow[\text{hexane/toluene}]{\text{Chiral catalyst } \mathbf{1a}, \text{Ti}(\text{O}^i\text{Pr})_4} \text{R}^1\text{-CH(OH)-R}^2$$

Entry <sup>a</sup>	R <sup>1</sup> CHO	R <sup>2</sup> <sub>2</sub> Zn	Time (h)	Yield (%)	ee (%) <sup>b</sup>	Config.
1	PhCHO	Me <sub>2</sub> Zn	2	78	97 <sup>c</sup>	S-(−)
2	PhCHO	Et <sub>2</sub> Zn	5	90	96 <sup>d</sup>	S-(−)
3	2-MeOC <sub>6</sub> H <sub>4</sub> CHO	Et <sub>2</sub> Zn	1	85	98 <sup>e</sup>	S-(−)
4	( <i>E</i> )-PhCH=CHCHO	Et <sub>2</sub> Zn	1	87	91 <sup>f</sup>	S-(−)
5	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>7</sub> CHO	Et <sub>2</sub> Zn	5	45	79 <sup>g</sup>	S-(+)

<sup>a</sup> PhCHO/Et<sub>2</sub>Zn/**1a**/Ti(O<sup>*i*</sup>Pr)<sub>4</sub> = 1/3/0.15/1.2. <sup>b</sup> Determined by HPLC analysis using chiral column (4×250 mm, 254 nm UV detector). <sup>c</sup> Daicel Chiralcel OD, room temperature, eluent: 3% propan-2-ol in hexane, flow rate: 1.0 ml/min, retention time (min), 12 for minor (*R*)-isomer, 14 for major (*S*)-isomer. <sup>d</sup> See footnote b in Table I. <sup>e</sup> Daicel Chiralcel OB, room temperature, eluent: 3% propan-2-ol in hexane, flow rate: 0.5 ml/min, retention time (min), 21 for major (*S*)-isomer, 32 for minor (*R*)-isomer. <sup>f</sup> Daicel Chiralcel OD, room temperature, eluent: 10% propan-2-ol in hexane, flow rate: 0.5 ml/min, retention time (min), 16 for minor (*R*)-isomer, 24 for major (*S*)-isomer. <sup>g</sup> Determined as benzoate. Daicel Chiralpak OT(+); 0°C, eluent: MeOH, flow rate: 0.2 ml/min, retention time (min), 25 for major (*S*)-isomer, 34 for minor (*R*)-isomer.

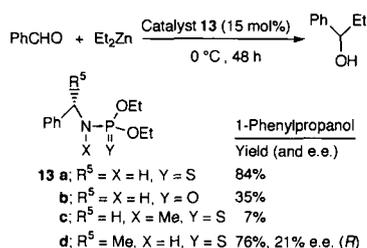
selective ethylation of 2-methoxybenzaldehyde afforded the corresponding alcohol with a very high (98%) *ee* in 85% yield (entry 3). The  $\alpha,\beta$ -unsaturated aldehyde, (*E*)-3-phenylprop-2-enal, afforded the enantiomerically enriched allyl alcohol with 91% *ee* (entry 4). The ethylation of an aliphatic aldehyde, nonanal, produced (*S*)-undecan-3-ol in moderate *ee* (entry 5).

It should be noted that norephedrine is readily available in either enantiomeric form. Thus, by using (1*R*,2*S*)-**1a** instead of (1*S*,2*R*)-**1a**, (*R*)-alcohols with equally high *ees* should be obtained with the same yields. It should also be noted that the chiral catalyst can be recovered. For example, **7** was recovered in 68% yield by silica-gel TLC purification.

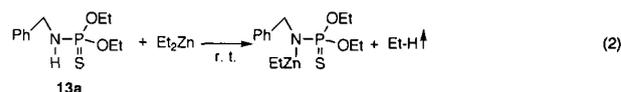
Compound **1a**, in the absence of  $\text{Ti}(\text{O}^i\text{Pr})_4$ , catalyzes the addition of dialkylzinc to benzaldehyde (Table III, entry 13). Because **1a** contains both a hydroxyl and thiophosphoramidate group, we examined the catalytic activity of the phosphoramidate group (and its thio analog) using the simple achiral and chiral (enantiomerically pure) diethyl *N*-mono- and di-alkyl (thio)phosphoramidates.

It was found that thiophosphoramidates and phosphoramidates [(RO)<sub>2</sub>P(X)NHR'] catalyze the addition of dialkylzinc to benzaldehyde. In fact, achiral diethyl *N*-benzylthiophosphoramidate (**13a**) (0.15 eq.) catalyzed the addition of diethylzinc to benzaldehyde at 0°C for 48 h in the absence of  $\text{Ti}(\text{O}^i\text{Pr})_4$  to produce racemic 1-phenylpropan-1-ol in 84% (Scheme 2).

Diethyl *N*-benzylphosphoramidate (**13b**), the oxygen analog of **13a**, gave the alcohol in 35%. On the other hand, the catalytic activity of diethyl *N*-benzyl-*N*-methylthiophosphoramidate (**13c**) without a N-H moiety was very low (7% yield). Thus, the N-H moiety is necessary for



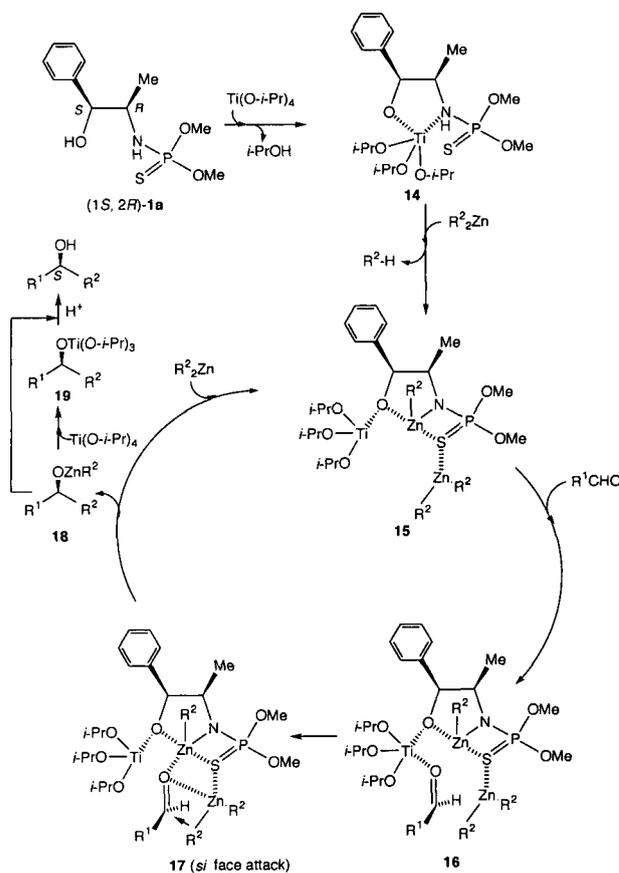
Scheme 2. Catalyzed addition by (thio)phosphoramidate



the catalytic activity. These results are in accordance with the results using chiral catalysts **1a** (with N-H) and **12** (with N-Me) (Table I, entries 1 and 8). In addition, chiral (enantiomerically pure) (*S*)-diethyl *N*-(1-phenylethyl)thiophosphoramidate (**13d**) (0.15 eq.), prepared from (*S*)-(1-phenylethyl)amine, in the absence of  $\text{Ti}(\text{O}^i\text{Pr})_4$  afforded optically active (*R*)-1-phenylpropan-1-ol with 21% *ee* in 76% yield.

The treatment of diethyl *N*-benzylthiophosphoramidate (**13a**) with Et<sub>2</sub>Zn at room temperature produced one molar equivalent of ethane, most probably as a result of the deprotonation from the N-H moiety (Eqn. 2).

On the other hand, the NMR analysis of the mixture of the equimolar amount of the catalyst **1a** and  $\text{Ti}(\text{O}^i\text{Pr})_4$  in CCl<sub>4</sub> at room temperature for 1 h revealed that about 60% of the methine proton signal ( $\delta$  4.78 ppm) of the alcohol moiety shifted downfield to  $\delta$  5.55 ppm as a result of the formation of titanium alkoxide **14** (Scheme 3) (in practical asymmetric reactions, other solvents than CCl<sub>4</sub> shown in Table IV were used). Because the molar ratio of catalyst **1a** and  $\text{Ti}(\text{O}^i\text{Pr})_4$  varies between 1/8 and 1/24 in practical asymmetric synthesis, the yield of the complex **14** is considered to be much higher than 60%. In addition, when equimolar amounts of catalyst **1a** and  $\text{Ti}(\text{O}^i\text{Pr})_4$  were heated in CCl<sub>4</sub> for 30 min, distilling CCl<sub>4</sub> and the formed <sup>*i*</sup>PrOH, all of **1a** became titanium alkoxide **14**. In asymmetric synthesis using 3 eq. of dialkylzinc, the temperature of the formation of titanium complex **14** did not affect the enantioselectivity.



Scheme 3.

From these observations, we postulate one of the possible structures of the reactive intermediates shown in Scheme 3. The addition of dialkylzinc to **14** may form the complex **15** as a result of the deprotonation of **14** and the coordination between the sulfur atom (soft Lewis base)<sup>24</sup> of **14** with the zinc atoms (Lewis acid of the hard and soft border line). The affinity between sulfur and zinc atoms is strong<sup>11,25</sup>. Subsequently, the nucleophilicity of the alkyl group of the dialkylzinc increases. The titanium atom (hard Lewis acid)<sup>24</sup> may control the steric course of the approach of the aldehyde shown as **16** by coordination with the oxygen atom (hard Lewis base) of the aldehyde. The aldehyde approaches from the lower side of the chiral (enantiomerically pure) complex in a direction such that the large substituent ( $R^1$ ) is farthest from the chiral complex. The alkyl ( $R^2$ ) group of the activated (coordinated) dialkylzinc then attacks the aldehyde from the *Si* face shown as **17** and the chiral (enantiomerically enriched) zinc alkoxide **18** dissociates. The hydrolysis of **18** or of the titanium alkoxide **19** [formed by the reaction of **18** with  $Ti(O^iPr)_4$ , as pointed out by Seebach<sup>26</sup>] affords the enantiomerically enriched (*S*)-*sec*-alcohol (when the priority order is  $R^1 > R^2$ ). The chiral (enantiomerically pure) complex **15** regenerates by coordination of a new dialkylzinc molecule.

## Conclusions

As described, enantiomerically pure hydrogen phosphoramidates and phosphinamides (and their thio analogs) derived from norephedrine and other enantiomerically pure amino alcohols catalyze the enantioselective addition of dialkylzinc to aldehydes in the presence of titanium tetraisopropoxide. This result may open the way to the use of thiophosphoramidates, phosphoramidates, thiophosphinamides and phosphinamides as chiral catalysts in asymmetric synthesis.

## Experimental

<sup>1</sup>H-NMR spectra were recorded on a Hitachi R-1200 (60 MHz) or a JEOL JNM-EX270L (270 MHz) spectrometers with tetramethylsilane ( $\delta$  0 ppm) as internal standard. IR spectra were recorded on a Hitachi 260-30 or Horiba FT300 spectrophotometer. Optical rotations were measured using JASCO DIP-181 or DIP-360 polarimeters. Melting points are uncorrected. All reactions were carried out under an argon atmosphere.

### (1*S*,2*R*)-*N*-(*O*,*O*-Dimethylthiophosphoryl)norephedrine (**1a**)

Dimethyl chlorothiophosphate (4.82 g, 30 mmol) was added to a solution of (1*S*,2*R*)-(+)-norephedrine (6.50 g, 40 mmol) and triethylamine ( $Et_3N$ ) (4.05 g, 40 mmol) in  $CH_2Cl_2$  (5 ml) at  $-30^\circ C$ . After stirring for 15 min at  $-30^\circ C$ , 10% aq. citric acid was added. The mixture was extracted with  $CH_2Cl_2$ , and the extract was dried over  $Na_2SO_4$ , and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/AcOEt 3/1). **1a** (6.53 g, 79% yield) was obtained as an oil;  $[\alpha]_D +13$  (c 1.0, MeOH). <sup>1</sup>H-NMR (60 MHz,  $CDCl_3$ ):  $\delta$  0.95–1.10 d, *J* 6.3 Hz, 3H, -CH<sub>3</sub>; 2.68–2.77, d, 1H, -OH; 2.99–3.36, br, 1H, -C-CH-N; 3.69, dd, *J* 13.7, 1.1 Hz, 6H, P-O-CH<sub>3</sub>; 3.88–4.42, m, 1H, -NH; 4.71–4.88, m, 1H, -C-CH-Ph; 7.32, s, 5H, -Ph. IR (neat, NaCl): 3350, 2970, 2940, 1700, 1440, 1400, 1170, 1130, 1010, 960, 890, 840, 800, 740, 700, 670  $cm^{-1}$ . HRMS ( $C_{11}H_{18}NO_3PS$ ): calcd. 275.0746; found 275.0754.

### (1*S*,2*R*)-*N*-(*O*,*O*-Diethylthiophosphoryl)norephedrine (**1b**)

Diethyl chlorothiophosphate (1.92 g, 10.2 mmol) was added to a solution of (1*S*,2*R*)-(+)-norephedrine (2.26 g, 15.0 mmol) and  $Et_3N$  (3.05 g, 30.1 mmol) in toluene (7.5 ml) at  $-30^\circ C$ . After stirring for 2 h at  $-30^\circ C$ , 10% aq. citric acid and  $Et_2O$  were added. The organic layer was washed with 10% aq. citric acid (3 times) and saturated aq. NaCl, dried over  $Na_2SO_4$ , and concentrated under reduced pres-

sure. The residue was purified by column chromatography (silica gel, hexane/AcOEt 3:1). **1b** (1.93 g, 62% yield) was obtained as an oil.  $[\alpha]_D -17$  (c 1.33, MeOH). <sup>1</sup>H-NMR (60 MHz,  $CDCl_3$ ):  $\delta$  0.91–1.10, d, *J* 6 Hz, 3H, -N-C-CH<sub>3</sub>; 1.15–1.50, t, *J* 7 Hz, 6H, -O-C-CH<sub>3</sub>; 2.61–2.81, br, 1H, -OH; 3.11–3.42, br, 1H, -C-CH-N; 3.45–3.90, m, 1H, -NH; 3.78–4.35, m, 4H, -O-CH<sub>2</sub>-C; 4.68–4.89, br, 1H, -O-CH-Ph; 7.25, s, 5H, -Ph. IR (neat, NaCl): 3400, 2980, 2900, 1450, 1400, 1300, 1200, 1140, 1040, 960, 900, 830, 800, 710  $cm^{-1}$ . HRMS ( $C_{13}H_{22}NO_3PS$ ): calcd. 303.10596; found 303.1042.

### (1*S*,2*R*)-*N*-(Dimethylthiophosphinyl)norephedrine (**2a**)

This material was synthesized by the procedure described for **1a**, except that the following materials were employed: (1*S*,2*R*)-(+)-norephedrine (0.454 g, 3 mmol); dimethylthiophosphinyl chloride (0.257 g, 2 mmol);  $Et_3N$  (0.405 g, 4 mmol). Compound **2a** (0.413 g, 85% yield) was obtained as an oil.  $[\alpha]_D -16$  (c 0.93, MeOH). <sup>1</sup>H-NMR (60 MHz,  $CDCl_3$ ):  $\delta$  0.91–1.15, d, *J* 6.6 Hz, 3H, -N-C-CH<sub>3</sub>; 1.81, d, *J* 12.2 Hz, 6H, -P-CH<sub>3</sub>; 2.00–2.45, m, 1H, -OH; 2.95–3.22, br, 1H, -N-CH-C; 3.35–3.82, m, 1H, -NH; 4.66–4.85, br, 1H, -O-CH-Ph; 7.25, s, 5H, -Ph. IR (neat, NaCl): 3300, 2970, 1490, 1400, 1300, 1140, 970, 930, 730, 700  $cm^{-1}$ . HRMS ( $C_{11}H_{18}NOPS$ ): calcd. 243.0848; found 243.0843.

### (1*S*,2*R*)-*N*-(Diphenylthiophosphinyl)norephedrine (**2b**)

(1*S*,2*R*)-(+)-Norephedrine hydrochloride (1.88 g, 10 mmol) was added to a solution of 2M aq. NaOH (15 ml, 30 mmol) and  $Et_2O$  (30 ml). Diphenylthiophosphinyl chloride was added to the mixture at  $0^\circ C$ . After stirring for 4 h at room temperature, the mixture was extracted with  $CH_2Cl_2$ . The extract was dried over  $Na_2SO_4$ , and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/AcOEt 3/1). **2b** (2.98 g, 81% yield) was obtained as a crystalline solid; m.p. 109–110°C;  $[\alpha]_D -24$  (c 1.0, MeOH). <sup>1</sup>H-NMR (60 MHz,  $CDCl_3$ ):  $\delta$  0.92–1.15, d, *J* 7 Hz, 3H, -N-C-CH<sub>3</sub>; 1.42–1.94, m, 1H, -OH; 3.09–3.29, d, 1H, -N-CH-C; 3.30–4.02, m, 1H, -NH; 4.89–5.15, m, 1H, -O-CH-Ph; 7.07–8.03, m, 15H, -Ph. IR (KBr): 3600, 3400, 3050, 2980, 1450, 1410, 1320, 1300, 1140, 1120, 1090, 1020, 980, 910, 840, 760, 730, 700  $cm^{-1}$ . HRMS ( $C_{21}H_{22}NOPS$ ): calcd. 367.1162; found 367.1191.

### (1*S*,2*R*)-*N*-(*O*,*O*-Dimethylphosphoryl)norephedrine (**3a**)

This material was synthesized by the procedure described for **1a**, except that the following materials and conditions were employed: (1*S*,2*R*)-(+)-norephedrine (1.51 g, 10.0 mmol);  $Et_3N$  (5.08 g, 50.2 mmol);  $CH_2Cl_2$  15 ml; dimethyl chlorophosphate (1.61 g, 11.1 mmol)<sup>27</sup>; reaction time: 1.25 h; purification: column chromatography (silica gel, hexane/AcOEt 1/1). Compound **3a** (1.64 g, 63% yield) was obtained as an oil;  $[\alpha]_D +0.6$  (c 3.0, MeOH). <sup>1</sup>H-NMR (60 MHz,  $CDCl_3$ ):  $\delta$  0.98, t, 3H, -N-C-CH<sub>3</sub>; 3.62, m, 3H, -N-CH-C-OH, -NH; 3.7, dd, *J* 11.6, 1.2 Hz, 6H, -P-O-CH<sub>3</sub>; 4.80, m, 1H, -O-CH-Ph; 7.30, s, 5H, -Ph. IR (neat, NaCl): 3380, 2975, 1500, 1450, 1245, 1040, 845, 760, 710  $cm^{-1}$ . HRMS ( $C_{11}H_{18}NO_4P$ ): calcd. 259.0974; found 259.0966.

### (1*S*,2*R*)-*N*-(*O*,*O*-Diethylphosphoryl)norephedrine (**3b**)

This material was synthesized by the same procedure as **1b** except that the following materials and conditions were employed: (1*S*,2*R*)-(+)-norephedrine (2.27 g, 15.0 mmol); toluene 7 ml;  $Et_3N$  (3.05 g, 30.1 mmol); diethyl chlorophosphate (1.73 g, 10.0 mmol); reaction time: 40 min; purification: column chromatography (silica gel, AcOEt). **3b** (2.06 g, 71% yield) was obtained as an oil;  $[\alpha]_D -5$  (c 1.07, MeOH). <sup>1</sup>H-NMR (60 MHz,  $CDCl_3$ ):  $\delta$  0.88–1.09, d, *J* 6.4 Hz, 3H, -N-C-CH<sub>3</sub>; 1.12–1.55, t, *J* 7 Hz, 6H, -P-O-C-CH<sub>3</sub>; 3.02–3.55, br, 1H, -OH; 3.55–3.62, br, 1H, -N-CH-C; 3.70–4.48, m, 5H, -P-O-CH<sub>2</sub>-C-, -NH; 4.73–4.85, d, 1H, -O-CH-Ph; 7.25, s, 5H, -Ph. IR (neat, NaCl): 3300, 2990, 2900, 1740, 1450, 1400, 1380, 1300, 1210, 1140, 1050, 970, 810, 750, 710  $cm^{-1}$ . HRMS ( $C_{13}H_{22}NO_4P$ ): calcd. 287.1288; found 287.1273.

### (1*S*,2*R*)-*N*-(*O*,*O*-Diisopropylphosphoryl)norephedrine (**3c**)

This material was synthesized by the same procedure as **1a** except that the following materials and conditions were employed: (1*S*,2*R*)-(+)-norephedrine (2.15 g, 14.2 mmol);  $Et_3N$  (4.31 g, 42.6 mmol);  $CH_2Cl_2$  15 ml; diisopropyl chlorophosphate (3.40 g, 16.9 mmol)<sup>27</sup>; reaction time: 50 min; purification: column chromatography (silica gel, AcOEt/MeOH 25/1). Compound **3c** (4.48 g, 100% yield) was

obtained as a crystalline solid; m.p. 60.5–62°C;  $[\alpha]_D -4.1$  (c 3.02, MeOH).  $^1\text{H-NMR}$  (60 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.00, d,  $J$  6 Hz, 3H, -N-C-CH<sub>3</sub>; 1.38, d,  $J$  6 Hz, 12H, -P-O-C-CH<sub>3</sub>; 3.70, br, 3H, -NH, -OH, -C-CH-N-; 4.69, m, 3H, -O-CH-Ph, -O-CH-Me<sub>2</sub>; 7.27, s, 5H, -Ph. IR (KBr): 3380, 2965, 1490, 1380, 1220, 985, 700  $\text{cm}^{-1}$ . HRMS ( $\text{C}_{15}\text{H}_{26}\text{NO}_4\text{P}$ ): calcd. 315.1601; found 315.1605.

(1*S*,2*R*)-*N*-(Dimethylphosphinyl)norephedrine (**4a**)

This material was synthesized by the same procedure as **1a** except that the following materials and conditions were employed: (1*S*,2*R*)-(+)-norephedrine (0.756 g, 5 mmol); Et<sub>3</sub>N (1.01 g, 10 mmol); dimethylphosphinyl chloride (0.562 g, 5 mmol); Compound **4a** (0.784 g, 69% yield) was obtained as a crystalline solid; m.p. 146–149°C;  $[\alpha]_D +18$  (c 1.0, MeOH).  $^1\text{H-NMR}$  (60 MHz,  $\text{CDCl}_3$ ):  $\delta$  0.90–1.11, d,  $J$  6.8 Hz, 3H, -N-C-CH<sub>3</sub>; 1.25–1.65, d,  $J$  14 Hz, 6H, -P-CH<sub>3</sub>; 1.90–3.00, m, 2H, -OH, -NH; 3.22–3.74, m, 1H, -N-CH-C; 4.55–4.70, br, 1H, -O-CH-Ph; 7.25, s, 5H, -Ph. IR (KBr): 3200, 2980, 2900, 1450, 1410, 1300, 1230, 1170, 1130, 1100, 1040, 930, 900, 870, 830, 760, 740, 700  $\text{cm}^{-1}$ . HRMS ( $\text{C}_{11}\text{H}_{18}\text{NO}_2\text{P}$ ): calcd. 227.1076; found 227.1093.

(1*S*,2*R*)-*N*-(Diphenylphosphinyl)norephedrine (**4b**)

This material was synthesized by the same procedure as **1a** except that the following materials were employed: (1*S*,2*R*)-(+)-norephedrine (1.13 g, 7.5 mmol); Et<sub>3</sub>N (1.01 g, 10 mmol); diphenylphosphinyl chloride (1.18 g, 5 mmol). Compound **4b** (1.38 g, 78% yield) was obtained as a crystalline solid; m.p. 152–153°C;  $[\alpha]_D -29$  (c 1.0, MeOH).  $^1\text{H-NMR}$  (60 MHz,  $\text{CDCl}_3$ ):  $\delta$  0.98–1.20, d,  $J$  5.6 Hz, 3H, -N-C-CH<sub>3</sub>; 3.06–3.69, m, 2H, -OH, -NH; 4.74–4.95, br, 1H, -N-CH-C; 5.41–6.01, m, 1H, -O-CH-Ph; 6.98–8.32, m, 15H, -Ph. IR (KBr): 3200, 1440, 1310, 1180, 1150, 1130, 1100, 1020, 1000, 970, 900, 840, 750, 730, 700  $\text{cm}^{-1}$ . HRMS ( $\text{C}_{21}\text{H}_{22}\text{NO}_2\text{P}$ ): calcd. 351.1390; found 351.1383.

(1*S*,2*R*)-2-[(*O,O*-Dimethylthiophosphoryl)amino]-1,2-diphenylethanol (**5**)

This material was synthesized by the same procedure as **1a** except that the following materials and conditions were employed: (1*S*,2*R*)-(+)-2-amino-1,2-diphenylethanol (0.213 g, 0.998 mmol); Et<sub>3</sub>N (0.407 g, 4.02 mmol); CH<sub>2</sub>Cl<sub>2</sub> 18 ml; dimethyl chlorothiophosphate (0.159 g, 0.998 mmol); purification: TLC (silica gel, hexane/AcOEt 3/1). Compound **5** (0.249 g, 74% yield) was obtained as a crystalline material; m.p. 91.0–91.5°C;  $[\alpha]_D^{23} +15.4$  (c 2.0, MeOH).  $^1\text{H-NMR}$  (60 MHz,  $\text{CDCl}_3$ ):  $\delta$  2.64, br, 1H, -OH; 3.44, dd,  $J$  13.9, 11.6 Hz, 6H, -P-O-CH<sub>3</sub>; 4.48, m, 3H, -O-CH-Ph, -N-CH-Ph, -NH; 7.24, m, 10H, -Ph. IR (KBr): 3380, 3000, 2915, 2870, 2825, 1595, 1485, 1440, 1405, 1337, 1290, 1250, 1180, 1085, 1050, 1020, 963, 855, 815, 785, 698, 638, 603, 565, 470  $\text{cm}^{-1}$ . HRMS ( $\text{C}_{16}\text{H}_{20}\text{NO}_3\text{PS}$ ): calcd. 337.0903; ( $\text{C}_{16}\text{H}_{20}\text{NO}_3\text{PS} - \text{H}_2\text{O}$ ): calcd. 319.0797; found 319.0791.

(*S*)-1-[(*O,O*-Dimethylthiophosphoryl)amino]propan-2-ol (**6**)

This material was synthesized by the same procedure as **1a** except that the following materials and conditions were employed: (*S*)-(+)-1-amino-propan-2-ol (0.0795 g, 1.06 mmol); Et<sub>3</sub>N (0.603 g, 5.95 mmol); CH<sub>2</sub>Cl<sub>2</sub> 1 ml; dimethyl chlorothiophosphate (0.160 g, 0.996 mmol); reaction time: 1½ h; purification: TLC (silica gel, hexane/AcOEt 3/1). Compound **6** (0.146 g, 74% yield) was obtained as an oil;  $[\alpha]_D^{23} +10.3$  (c 5.6, MeOH).  $^1\text{H-NMR}$  (60 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.25, d,  $J$  5.8 Hz, 3H, -O-C-CH<sub>3</sub>; 3.10, m, 3H, -OH, -N-CH<sub>2</sub>-C; 3.73, d,  $J$  13.6 Hz, 6H, -P-O-CH<sub>3</sub>; 3.90, m, 2H, -O-CH, -NH. IR (neat, NaCl): 3370, 2949, 1630, 1458, 1182, 1042, 949, 817, 526  $\text{cm}^{-1}$ . HRMS ( $\text{C}_5\text{H}_{14}\text{NO}_3\text{PS}$ ): calcd. 199.0433; found 199.0437.

(*R*)-2-[(*O,O*-Dimethylthiophosphoryl)amino]-1-phenylethanol (**7**)

This material was synthesized by the same procedure as **1a** except that the following materials and conditions were employed: (*R*)-2-amino-1-phenylethanol (0.134 g, 0.977 mmol)<sup>28</sup>; Et<sub>3</sub>N (0.595 g, 5.88 mmol); CH<sub>2</sub>Cl<sub>2</sub> 2 ml; dimethyl chlorothiophosphate (0.204 g, 1.27 mmol); reaction time: 3 h 10 min; purification: TLC (silica gel, hexane/AcOEt 3/1). Compound **7** (0.161 g, 63% yield) was obtained as an oil;  $[\alpha]_D^{26} -5.6$  (c 5.62, MeOH).  $^1\text{H-NMR}$  (60 MHz,  $\text{CDCl}_3$ ):  $\delta$  3.23, m, 3H, -C-CH<sub>2</sub>-N, -OH; 3.66, dd,  $J$  1.38, 2.8 Hz, 6H, -P-O-CH<sub>3</sub>; 3.88, br, 1H, -NH; 4.76, q, 1H, -O-CH-Ph; 7.38, s, 5H, -Ph. IR (neat, NaCl): 3410, 2950, 2840, 1590, 1500, 1450, 1400, 1180, 1024, 940, 820, 700  $\text{cm}^{-1}$ . HRMS ( $\text{C}_{10}\text{H}_{16}\text{NO}_3\text{PS}$ ): calcd. 261.0590; found 261.0588.

(*S*)-2-[(*O,O*-Dimethylthiophosphoryl)amino]propan-1-ol (**8a**)

This material was synthesized by the same procedure as **1a** except that the following materials and conditions were employed: (*S*)-(+)-2-amino-propan-1-ol (0.225 g, 2.99 mmol); Et<sub>3</sub>N (1.82 g, 17.9 mmol); CH<sub>2</sub>Cl<sub>2</sub> 2 ml; dimethyl chlorothiophosphate (0.621 g, 3.87 mmol); reaction time: 2 h; purification: TLC (silica gel, hexane/AcOEt 1/1). Compound **8a** (0.356 g, 59% yield) was obtained as an oil;  $[\alpha]_D^{23} +4.4$  (c 3.96, MeOH).  $^1\text{H-NMR}$  (60 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.15, d,  $J$  6 Hz, 3H, -N-C-CH<sub>3</sub>; 3.00, br, 1H, -OH; 3.50, m, 4H, -N-CH-C, -C-CH<sub>2</sub>-O, -NH; 3.69, d,  $J$  13.8 Hz, 6H, -P-O-CH<sub>3</sub>. IR (neat, NaCl): 3330, 2925, 2855, 2830, 1410, 1175, 1140, 1015, 965, 885, 825, 800, 635, 470  $\text{cm}^{-1}$ . HRMS ( $\text{C}_5\text{H}_{14}\text{NO}_3\text{PS}$ ): calcd. 199.0433; found 199.0413.

(*S*)-2-[(*O,O*-Dimethylthiophosphoryl)amino]-3-methylbutan-1-ol (**8b**)

This material was synthesized by the same procedure as **1a** except that the following materials and conditions were employed: (*S*)-(+)-2-amino-3-methylbutan-1-ol (0.309 g, 3.00 mmol); Et<sub>3</sub>N (1.82 g, 17.9 mmol); CH<sub>2</sub>Cl<sub>2</sub> 2 ml; dimethyl chlorothiophosphate (0.621 g, 3.87 mmol); reaction time: 2 h 10 min; purification: TLC (silica gel, hexane/AcOEt 1/1). Compound **8b** (0.269 g, 40% yield) was obtained as an oil;  $[\alpha]_D^{27} -16.1$  (c 3.0, MeOH).  $^1\text{H-NMR}$  (60 MHz,  $\text{CDCl}_3$ ):  $\delta$  0.90, d,  $J$  6 Hz, 6H, -C-(CH<sub>3</sub>)<sub>2</sub>; 1.76, quint, 1H, -C-CH-Me<sub>2</sub> 3.50, m, 5H, HO-CH<sub>2</sub>-CH-NH; 3.69, d,  $J$  14.4 Hz, 6H, -P-O-CH<sub>3</sub>. IR (neat, NaCl): 3320, 3000, 1570, 1340, 1185, 950  $\text{cm}^{-1}$ . HRMS ( $\text{C}_7\text{H}_{18}\text{NO}_3\text{PS}$ ): calcd. 227.0746; found 227.0745.

(*S*)-2-[(*O,O*-Dimethylthiophosphoryl)amino]-4-methylpentan-1-ol (**8c**)

This material was synthesized by the same procedure as **1a** except that the following materials and conditions were employed: (*S*)-(+)-2-amino-4-methylpentan-1-ol, (0.357 g, 3.04 mmol); Et<sub>3</sub>N (1.82 g, 17.9 mmol); CH<sub>2</sub>Cl<sub>2</sub> 2 ml; dimethyl chlorothiophosphate (0.529 g, 3.29 mmol); reaction time: 2 h 15 min; purification: TLC (silica gel, hexane/AcOEt 3/1). Compound **8c** (0.491 g, 67% yield) was obtained as an oil;  $[\alpha]_D^{28} -24.4$  (c 3.0, MeOH).  $^1\text{H-NMR}$  (60 MHz,  $\text{CDCl}_3$ ):  $\delta$  0.92, d,  $J$  6.2 Hz, 6H, -C-C-(CH<sub>3</sub>)<sub>2</sub>; 1.58, m, 3H, -C-CH<sub>2</sub>-CH-Me<sub>2</sub>; 3.35, m, 5H, HO-CH<sub>2</sub>-CH-NH; 3.72, d,  $J$  13.8 Hz, 6H, -P-O-CH<sub>3</sub>. IR (neat, NaCl): 3300, 2925, 1410, 1020, 780  $\text{cm}^{-1}$ . HRMS ( $\text{C}_8\text{H}_{20}\text{NO}_3\text{PS}$ ): calcd. 241.0903; found, 241.0911.

(*S*)-2-[(*O,O*-Dimethylthiophosphoryl)amino]-2-phenylethanol (**8d**)

This material was synthesized by the same procedure as **1a** except that the following materials and conditions were employed: (*S*)-(+)-2-amino-2-phenylethanol (0.133 g, 0.97 mmol); Et<sub>3</sub>N (0.610 g, 6.03 mmol); CH<sub>2</sub>Cl<sub>2</sub> 3 ml; dimethyl chlorothiophosphate (0.209 g, 1.30 mmol); reaction time: 22½ h; purification: TLC (silica gel, hexane/AcOEt 3/1). Compound **8d** (0.0406 g, 16% yield) was obtained as an oil;  $[\alpha]_D^{24} +46.8$  (c 2.1, MeOH).  $^1\text{H-NMR}$  (60 MHz,  $\text{CDCl}_3$ ):  $\delta$  2.12, br, 1H, -OH; 3.58, dd,  $J$  13.8, 13.8 Hz, 6H, -P-O-CH<sub>3</sub>; 3.84, m, 2H, -C-CH<sub>2</sub>-O; 4.40, m, 2H, -NH, -N-CH-Ph; 7.34, s, 5H, -Ph. IR (neat, NaCl): 3380, 2955, 1600, 1500, 1460, 1420, 1180, 1030, 810, 700  $\text{cm}^{-1}$ . HRMS ( $\text{C}_{10}\text{H}_{16}\text{NO}_3\text{PS} - \text{H}_2\text{O}$ ): calcd. 243.0484; found 243.0480.

(*R*)-2-[(*O,O*-Dimethylthiophosphoryl)amino]butan-1-ol (**9**)

This material was synthesized by the same procedure as **1a** except that the following materials and conditions were employed: (*R*)-(-)-2-aminobutan-1-ol (0.274 g, 3.07 mmol); Et<sub>3</sub>N (1.82 g, 17.9 mmol); CH<sub>2</sub>Cl<sub>2</sub> 2 ml; dimethyl chlorothiophosphate (0.621 g, 3.87 mmol); reaction time: 2 h; purification: TLC (silica gel, hexane/AcOEt 2/1). Compound **9** (0.419 g, 64% yield) was obtained as an oil;  $[\alpha]_D^{25} +13.1$  (c 2.2, MeOH).  $^1\text{H-NMR}$  (60 MHz,  $\text{CDCl}_3$ ):  $\delta$  0.95, t,  $J$  7 Hz, 3H, -CH<sub>3</sub>; 1.46, q,  $J$  6 Hz, 2H, -C-CH<sub>2</sub>-Me; 2.84, br, 1H, -OH; 3.30–3.54, m, 4H, -O-CH<sub>2</sub>-CH-NH; 3.76, d,  $J$  13.8 Hz, 6H, -P-O-CH<sub>3</sub>. IR (neat, NaCl): 3350, 2950, 1450, 1410, 1190, 1040, 820  $\text{cm}^{-1}$ . HRMS ( $\text{C}_6\text{H}_{16}\text{NO}_3\text{PS}$ ): calcd. 213.0590; found 213.0593.

(1*S*,2*S*)-2-[(*O,O*-Dimethylthiophosphoryl)amino]-3-methoxy-1-phenylpropan-1-ol (**10**)

This material was synthesized by the same procedure as **1a** except that the following materials and conditions were employed: (1*S*,2*S*)-

(+)-2-amino-3-methoxy-1-phenylpropan-1-ol (0.393 g, 2.17 mmol)<sup>29</sup>; Et<sub>3</sub>N (1.31 g, 12.9 mmol); CH<sub>2</sub>Cl<sub>2</sub> 2 ml; dimethyl chlorothiophosphate (0.449 g, 2.80 mmol); reaction time: 2 h 5 min; purification: TLC (silica gel, hexane/AcOEt 2/1). Compound **10** (0.505 g, 76% yield) was obtained as an oil; [ $\alpha$ ]<sub>D</sub><sup>25</sup> + 44.9 (c 2.0, MeOH), <sup>1</sup>H NMR (60 MHz, CDCl<sub>3</sub>):  $\delta$  3.37, m, 14H, -C-CH-N-, -C-O-CH<sub>3</sub>, -P-O-CH<sub>3</sub>, -C-CH<sub>2</sub>-O-, -OH, -NH; 4.96, s, 1H, -O-CH-Ph; 7.35, s, 5H, -Ph. IR (neat, NaCl): 3420, 2950, 1500, 1460, 1410, 1200, 1030, 815 cm<sup>-1</sup>. HRMS (C<sub>12</sub>H<sub>20</sub>NO<sub>4</sub>PS): calcd. 305.0852 (C<sub>12</sub>H<sub>20</sub>NO<sub>4</sub>PS + H<sup>+</sup>): calcd. 306.0930; found 306.0938.

(S)-2-[(O,O-Dimethylthiophosphoryl)amino]-1,1-diphenylpropan-1-ol (**11**)

Dimethyl chlorothiophosphate (0.159 g, 0.988 mmol) was added to a solution of (S)-2-amino-1,1-diphenylpropan-1-ol (0.172 g, 0.756 mmol) and Et<sub>3</sub>N (0.457 g, 4.52 mmol) in THF (2 ml) at 0°C. After stirring for 2½ h at 0°C, 10% aq. citric acid was added. The mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub>, and the extract dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated under reduced pressure. The residue was purified by TLC (silica gel, hexane/AcOEt 3/1). **11** (0.154 g, 58% yield) was obtained as a crystalline material; m.p. 91.5–93.5°C; [ $\alpha$ ]<sub>D</sub><sup>25</sup> – 13.2 (c 3.84, MeOH). <sup>1</sup>H NMR (60 MHz, CDCl<sub>3</sub>):  $\delta$  1.15, d, J 6.4 Hz, 3H, -N-C-CH<sub>3</sub>; 2.75, s, 1H, -OH; 3.39, dd, J 14, 0.9 Hz, br, 7H, -P-O-CH<sub>3</sub>, -NH; 4.45, m, 1H, -N-CH-C; 7.33, m, 10H, -Ph. IR (neat, NaCl): 3380, 2945, 1620, 1500, 1445, 1390, 1280, 1195, 1040, 980, 820, 700 cm<sup>-1</sup>. HRMS (C<sub>17</sub>H<sub>22</sub>NO<sub>3</sub>PS): calcd. 351.1060; found 351.1059.

(1R,2S)-N-(O,O-Dimethylthiophosphoryl)ephedrine (**12**)

This material was synthesized by the same procedure as **1a** except that the following materials and conditions were employed: (1R,2S)-(-)-ephedrine (2.46 g, 14.9 mmol); Et<sub>3</sub>N (3.01 g, 29.8 mmol); CH<sub>2</sub>Cl<sub>2</sub> 5 ml; dimethyl chlorothiophosphate (0.793 g, 4.94 mmol); reaction time: 15 min; purification: column chromatography (silica gel, hexane/AcOEt 3/1). Compound **12** (0.693 g, 48% yield) was obtained as a crystalline material; m.p. 51–52.5°C; [ $\alpha$ ]<sub>D</sub><sup>25</sup> – 8.2 (c 3.0, MeOH). <sup>1</sup>H NMR (60 MHz, CDCl<sub>3</sub>):  $\delta$  1.20, d, J 6.6 Hz, 3H, -N-C-CH<sub>3</sub>; 2.58, d, J 10.7, s, 4H, -N-CH<sub>3</sub>, -OH; 3.41, dd, J 13.7, 13.7 Hz, 6H, -P-O-CH<sub>3</sub>; 4.32, quint, 1H, -N-CH-C; 4.70, d, J 5.8 Hz, 1H, s, -O-CH-Ph; 7.40, s, 5H, -Ph. IR (neat, NaCl): 3569, 2942, 1500, 1456, 1350, 1259, 1160, 1025, 891, 817, 769, 700, 600 cm<sup>-1</sup>. HRMS (C<sub>12</sub>H<sub>20</sub>NO<sub>3</sub>PS): calcd. 289.0903 (C<sub>12</sub>H<sub>20</sub>NO<sub>3</sub>PS-H<sub>2</sub>O): calcd. 271.0797; found 271.0799.

Diethyl N-benzylthiophosphoramidate (**13a**)

Benzylamine (0.481 g, 4.49 mmol) was added to a solution of Et<sub>3</sub>N (0.908 g, 8.97 mmol) and diethyl chlorothiophosphate (0.564 g, 2.99 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (4 ml) at 0°C. After stirring for 1 h 45 min at 0°C, 10% aq. citric acid and Et<sub>2</sub>O were added. The organic layer was washed with 10% aq. citric acid (3 times) and saturated aq. NaCl, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated under reduced pressure. The residue was purified by TLC (silica gel, hexane/AcOEt 5/1). Compound **13a** (0.631 g, 81% yield) was obtained as an oil. <sup>1</sup>H NMR (60 MHz, CDCl<sub>3</sub>):  $\delta$  1.33, t, J 6.8 Hz, 6H, -P-O-C-CH<sub>3</sub>; 3.48, br, 1H, -NH; 4.11, m, 6H, -CH<sub>2</sub>-Ph, -P-O-CH<sub>2</sub>-; 7.32, s, 5H, -Ph. IR (neat, NaCl): 3370, 2945, 1440, 1380, 1010, 945, 780, 680 cm<sup>-1</sup>. HRMS (C<sub>11</sub>H<sub>18</sub>NO<sub>2</sub>PS): calcd. 259.0797; found 259.0785.

Diethyl N-benzylphosphoramidate (**13b**)

This material was synthesized by the same procedure as **13a** except that the following materials and conditions were employed: benzylamine (0.481 g, 4.49 mmol); Et<sub>3</sub>N (0.908 g, 8.97 mmol); CH<sub>2</sub>Cl<sub>2</sub> 4 ml; diethyl chlorophosphate (0.513 g, 2.98 mmol); reaction time: 2 h; purification: TLC (silica gel, AcOEt). Compound **13b** (0.477 g, 65% yield) was obtained as an oil. <sup>1</sup>H NMR (60 MHz, CDCl<sub>3</sub>):  $\delta$  1.31, t, J 7.2 Hz, 6H, -P-O-C-CH<sub>3</sub>; 3.39, br, 1H, -NH; 4.08, m, 6H, -CH<sub>2</sub>-Ph, -P-O-CH<sub>2</sub>-; 7.33, s, 5H, -Ph. IR (neat, NaCl): 3200, 2950, 2880, 1440, 1220, 1030, 950, 855, 790, 725, 690 cm<sup>-1</sup>. HRMS (C<sub>11</sub>H<sub>18</sub>NO<sub>3</sub>P): calcd. 243, 1025; found 243.1031.

Diethyl N-benzyl-N-methylthiophosphoramidate (**13c**)

This material was synthesized by the same procedure as **13a** except that the following materials and conditions were employed: N-benzylmethylamine (0.545 g, 4.49 mmol); Et<sub>3</sub>N (0.908 g, 8.97 mmol); CH<sub>2</sub>Cl<sub>2</sub> 4 ml; diethyl chlorothiophosphate (0.564 g, 2.99 mmol); reaction time: 2 h; purification: TLC (silica gel, hexane/AcOEt 7/1). Compound **13c** (0.729 g, 89% yield) was obtained as an oil. <sup>1</sup>H

NMR (60 MHz, CDCl<sub>3</sub>):  $\delta$  1.35, t, J 7 Hz, 6H, -P-O-C-CH<sub>3</sub>; 2.63, d, J 10.6 Hz, 3H, -N-CH<sub>3</sub>; 4.10, quint, 4H, -P-O-CH<sub>2</sub>-C-; 4.37, d, 2H, -CH<sub>2</sub>-Ph; 7.33, s, 5H, -Ph. IR (neat, NaCl): 2975, 2900, 1600, 1500, 1470, 1450, 1390, 1215, 1135, 1020, 960, 800, 730, 700, 635 cm<sup>-1</sup>. HRMS (C<sub>12</sub>H<sub>20</sub>NO<sub>2</sub>PS): calcd. 273.0954; found 273.0946.

(S)-Diethyl N-(1-phenylethyl)thiophosphoramidate (**13d**)

This material was synthesized by the same procedure as **13a** except that the following materials and conditions were employed: (S)-(-)-1-phenylethylamine (0.54 g, 4.47 mmol); Et<sub>3</sub>N (0.908 g, 8.97 mmol); toluene 4 ml; diethyl chlorothiophosphate (0.564 g, 2.99 mmol); reaction time: 2 h 10 min; purification: TLC (silica gel, dichloromethane/carbon-tetrachloride 1/2). Compound **13d** (0.512 g, 63% yield) was obtained as an oil; [ $\alpha$ ]<sub>D</sub><sup>22</sup> – 38.1 (c 5.98, MeOH). <sup>1</sup>H NMR (60 MHz, CDCl<sub>3</sub>):  $\delta$  1.22, m, 9H, -P-O-C-CH<sub>3</sub>, -N-C-CH<sub>3</sub>; 3.92, m, 6H, -NH-CH-Ph, -P-O-CH<sub>2</sub>-; 7.25, s, 5H, -Ph. IR (neat, NaCl): 3280, 2970, 1490, 1445, 1410, 1390, 1290, 1200, 1025, 955, 800, 700, 650 cm<sup>-1</sup>. HRMS (C<sub>12</sub>H<sub>20</sub>NO<sub>2</sub>PS): calcd. 273.0954; found 273.0950.

Typical procedure for the enantioselective addition of dialkylzincs to aldehydes (Table VI, entry 2)

Ti(O<sup>i</sup>Pr)<sub>4</sub> (0.340 g, 1.19 mmol) was added to a solution of **1a** (0.041 g, 0.15 mmol) in toluene (2 ml) at room temperature. After 20 min, the mixture was cooled to –30°C and Et<sub>2</sub>Zn (1 M, 3 ml, 3 mmol) was added and stirred for 20 min at –30°C. Benzaldehyde (0.106 g, 1 mmol) was added, and the reaction mixture was stirred for 5 h at –30°C. Then the reaction was quenched with saturated aq. NH<sub>4</sub>Cl. The mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> and the extract dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated under reduced pressure. The residue was purified by TLC (silica gel, hexane/AcOEt 5/1) (S)-(-)-1-phenylpropan-1-ol (0.883 g, 90% yield, 96% ee) was obtained.

Acknowledgment

This work was financially supported by The SUT Special Grant for Research Promotion 1994–1995.

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