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Catalytic Enantioselective Alkylation of Benzaldehyde with Diethylzinc Using Chiral Nonracemic (Thio)-phosphoramidates

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Abstract: Two chiral nonracemic γ-amino alcohols, ephedrine thiol and the corresponding (thio)-phosphoramidates have been examined as catalysts for the enantioselective alkylation of benzaldehyde by diethylzinc. Addition of titanium tetraisopropoxide increases the yield as well as the enantioselectivity; 1-phenyl-propanol is obtained in up to 98% yield and *e.e.*
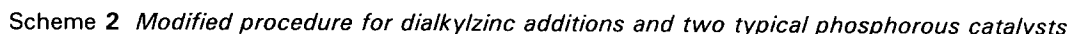Copyright © 1996 Published by Elsevier Science Ltd

Dialkylzinc reagents require an additive such as magnesium halide or, alternatively, amino alcohol or amino thiol ligands in order to add to aldehydes in reasonable yield.[1] On the use of catalytic amounts of *chiral nonracemic* amino alcohols[2] like **1-2** or amino thiols[3] **3-5** *enantioselective* alkylation takes place, affording the desired alcohols in moderate to high *e.e.'s* and yields.[4] The reaction of benzaldehyde to form 1-phenyl-propanol is given as example in Scheme **1**.
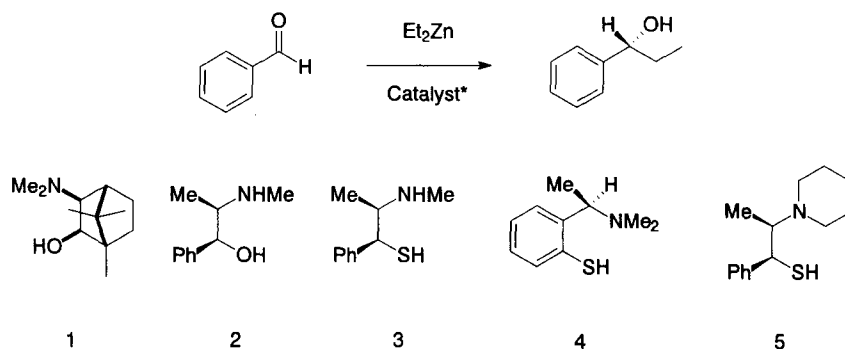
Scheme **1** *Diethylzinc addition to benzaldehyde and examples of ligand systems*

Recently, nonracemic chiral sulfonamides[5] and diols[6] in the presence of *titanium tetraisopropoxide* were also shown to be efficient catalysts in the enantioselective addition of dialkylzinc reagents to aldehydes. The perspectives of this reaction were further improved with the reports of Soai and co-workers,[7] who introduced ephedra based (thio)-phosphoramidates **6** and (thio)-phosphinamides **7** as efficient catalysts (Scheme **2**).

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Scheme 2 *Modified procedure for dialkylzinc additions and two typical phosphorous catalysts*

We recently developed ligands based on γ-amino alcohols **8** and **9**[8] and the corresponding (thio)-phosphoramidates **10-13**[9] and **14-15**[10,11] (Scheme 3). These proved to be excellent catalysts in the borane mediated asymmetric reduction of prochiral ketones.[9]

8 R= H
9 R= Cl

10 R= H
12 R= Cl

11 R= H
13 R= Cl

14

15

Scheme 3 *Ligands 8-15*

We now find that the phosphorylated ligands also catalyse the stereoselective alkylation of benzaldehyde using the titanium isopropoxide/diethylzinc reagent mixture (*vide supra*). In order to understand the factors governing stereodifferentiation better, the 'original' diethylzinc reaction, that is to say without addition of Ti(OiPr)$_4$, was investigated as well.

Firstly, the effect of the (*thio*)-phosphoryl substituents on the nitrogen atom of the catalysts during the enantioselective addition of Et$_2$Zn to benzaldehyde in the presence of Ti(OiPr)$_4$ was examined. In practice, complexation with Ti(OiPr)$_4$ was carried out *in situ* by treatment of 1.0 mmol of ligand with 1.2 mmol of Ti(OiPr)$_4$ in 5 mL of toluene at room temperature. Subsequently, the mixture was cooled to -50°C and Et$_2$Zn (3 mmol) was slowly added. The mixture was allowed to reach 0°C, cooled again to -50°C and 1.0 mmol of benzaldehyde was slowly added. After stirring for 5 hrs at -20°C the reaction was quenched with saturated aqueous NH$_4$Cl solution, extracted with CH$_2$Cl$_2$, dried over Na$_2$SO$_4$ and taken to dryness. The crude samples allowed analysis by means of chiral GC (*vide infra*) or, alternatively, ^{31}P NMR after derivatization.[12] The results are collected in Table 1.

ligand	yield (%) 1-phenyl-propanol	e.e. (%)	Conf.
8	11	17	S
9	14	26	S
10	81	74	S
11	92	87	S
12	80	83	S
13	93	96	S
14	>98	>98	S
15	_a	_a	-
3	20	36	S

Table 1 *Enantiomeric excesses (%), conversions (%) and configuration of 1-phenyl-propanol in Et$_2$Zn/Ti(OiPr)$_4$ alkylations of benzaldehyde. ^{a}No reaction observed.*

Although all the phosphorous containing ligands appeared to be good catalysts for this addition, the thio ($P = S$) catalysts are the most efficient, both in terms of e.e. and yield.[13] Ligands 10 and 11 both give the S product with an e.e. of 74 and 87% and yield of 81 and 92%, respectively. Analogous observations were made for ligands 12 and 13, which provide 1-phenyl-propanol with respective e.e.'s of 83 and 96% and chemical yields of 80 and 93%. The best ligand tested so far, however, is phosphorylated thiol ephedrine 14, which gave alcohol in both e.e. (S configuration) and yield of over 98%, whereas thiol ephedrine 3 itself only gave product in moderate e.e. (36%) and very low yield (20%). It appeared not to be possible, however, to obtain 14 completely pure due to cyclization to 16. Moreover, during the catalysis severe product cyclization and degradation takes place (Scheme 4).
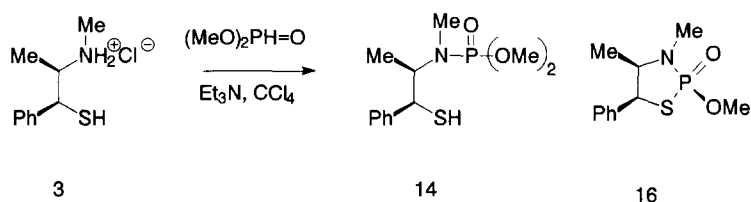
Scheme 4 *Cyclization of 14 during synthesis*

The non-phosphorylated ligands 8 and 9 appeared to be poor catalysts, as the product was obtained in low yield (11 and 14%) and low e.e. (17 and 26%). Ligand 15 failed to give any conversion at all.

To estimate the effects of the phosphorous substitution, the reactions were also carried out

with Et_2Zn as alkylating reagent but without additional $Ti(OiPr)_4$. Except for thiol ephedrine **3**, which afforded 1-phenyl-propanol in 89% *e.e.* and 87% yield, and ligands **8** and **9** which yielded results comparable to $Ti(OiPr)_4$ (see Table **1** and **2**), all other ligands gave only poor results. Moreover, the thio-phosphorous ligands **11** and **13** yielded the *S* alcohol, whereas ligands **10** and **12** gave rise to the formation of alcohol with the *R* configuration (!). The free ligands **8** and **9** also afforded the *S* alcohol.

ligand	yield (%) 1-phenyl-propanol	e.e. (%)	Conf.
8	13	25	*S*
9	17	14	*S*
10	9	5	*R*
11	23	37	*S*
12	13	15	*R*
13	27	48	*S*
14	>98	>98	*S*
15	_ª	_ª	-
3	87	89	*S*

Table 2 *Enantiomeric excesses (%), conversions (%) and configuration of 1-phenyl-propanol in Et_2Zn alkylations of benzaldehyde. ªNo reaction observed.*

These results clearly indicate that the phosphorous substituents have a marked effect on the stereochemical outcome and progress of the alkylation. NMR analysis of the mixtures of an equimolar amount of catalyst **10-13** and $Ti(OiPr)_4$ in toluene-d_8 revealed that the methylene protons undergo a collapse of the fine structure (an extreme *AB* system), and moreover large downfield shifts were observed bringing both resonances nearly together. For ligand **13** for example the *AB* system at δ 3.24 and 4.97 ppm shifts upon treatment with $Ti(OiPr)_4$ to δ 6.12-6.63 ppm, with severe line broadening. These observations are in agreement with the observations made by Saoi and co-workers.[7]

Contrary to the observations made by Soai, however, methylation of the nitrogen atom, *i.e.* starting with **3**, does not lead to a dramatic lowering of the *e.e.* In the Soai mechanism this amide proton is essential for the entire transformation. As stated, ligand **14** appears not to be stable under the employed reaction conditions. Also, since the possibility of *monomer-dimer*[3] equilibria is also present, we are not convinced that a single class of intermediates is responsible for the asymmetric addition. Therefore, we do not feel that we can provide a unique stereochemical model at this point.

In conclusion, the recently introduced ligands offer unique possibilities to influence stereocontrol. Clearly, the modification as firstly introduced by Soai and co-workers[7] by means

of simple phosphorylation increases the catalytic properties manyfold. Moreover, the facile synthesis and subsequent resolution of these ligands allows structural modification on several levels of synthesis.[14]

Experimental

General Remarks

All solvents were dried according to literature procedures. All reactions were carried out under an argon atmosphere, using Schlenck line conditions. ^{31}P, ^{1}H and ^{13}C NMR spectra were recorded on a Varian VXR 300 instrument thermostatted at 30 °C. The chemical shifts are expressed relative to CDCl$_3$ for ^{1}H NMR (at δ 7.26 ppm). Deuterated solvents were dried over an Al$_2$O$_3$ (activity I) column just prior to use. Et$_2$Zn solution in toluene (1M) and Ti(OiPr)$_4$ were obtained from Aldrich, used as received and stored under an Argon atmosphere.
Ligands **3** and **8-15** were prepared according to literature procedures.[3,9,10,11]

General procedure for stereoselective alkylation

Ligand (1.0 mmol) was dissolved in 5 mL of dry toluene at RT. Ti(OiPr)$_4$ (1.2 mmol) was slowly added and the mixture was stirred for 30 min. Subsequently, the mixture was cooled to -50°C and Et$_2$Zn (3 mmol) was slowly added. The mixture was allowed to reach 0°C, cooled again to -50°C and 1.0 mmol of benzaldehyde was slowly added. After stirring at -20°C for 5 hrs the reaction was quenched with saturated aqueous NH$_4$Cl solution, extracted with CH$_2$Cl$_2$, dried over Na$_2$SO$_4$ and taken to dryness. Enantiomeric excesses and conversions were determined using a Hewlett Packard 5890A chromatograph equipped with a 50 m. WCOT fused silica column coated with CP cyclodextrin-ß-2,3,6-M-19 (Chrompack no. 7501) and a Hewlett Packard HP 3396 series II integrator at 120 °C. Retention times (oven temp. 120 °C, flow 100 mL/min He): *R*-1-phenyl-propanol 27.5 min. and *S*-1-phenyl-propanol 28.2 min. Alternatively, an ^{31}P NMR based *e.e.* determination was performed.[12]

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