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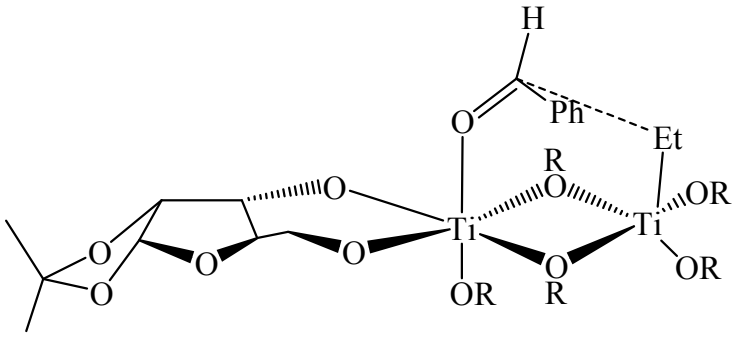

Enantioselective addition of diethylzinc to benzaldehyde catalyzed by an organometallic Ti(IV) compound and a xylose derivative

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Resumo

Um derivado do D-xylose, **1**, com $Ti(O^iPr)_4$ foi usado como um catalizador chiral na alquilação assimétrica do benzaldeído com dietylzinc (Et_2Zn) para produzir 1-fenyl-1-propanol no rendimento elevado (conversão de 90%) e na enantioseletividade moderado (45% ee (S)). As condições melhores (conversão e enantioseletividade) para o sistema catalítico formado por 1 equivalente do Ti (IV) e 10.0 % mol de **1** respeito ao benzaldeído em CH_2Cl_2 como o solvente, na temperatura ambiente. Na alquilação assimétrica do benzaldeído com composto 1 de Et_2Zn em uma quantidade substoichiometric com $Ti(O^iPr)_4$ formam um catalizador quiral do Ti(IV)-açucar o tipo que assegura uma conversão con bom rendimento e uma enantioselectividade da reação.

Abstract

A derivative of D-xylose, 1,2-O-isopropylidene-α-D-xylofuranose (**1**), with $Ti(O^iPr)_4$ was used as a chiral catalyst in the asymmetric alkylation of benzaldehyde with diethylzinc (Et_2Zn) for the high-yield production (90% conversion) and moderate enantioselectivity (45% ee (S)) of 1-phenyl-1-propanol.

Optimum conditions (conversion and enantioselectivity) for the catalytic system formed by **1** and Ti(IV) were 10.0 mol % of **1** and 1 equivalent of Ti(IV) with respect to benzaldehyde in CH_2Cl_2 as a solvent, at room temperature. In the asymmetric alkylation of benzaldehyde with Et_2Zn compound **1** in substoichiometric amount with $Ti(O^iPr)_4$ forms a chiral catalyst of the Ti(IV)-sugar type that ensures the good-yield conversion and the enantioselectivity of the reaction.

Keywords: diethylzinc, xylose derivative, Ti(IV), titanium

Introduction

1,2 enantioselective addition of organometallic compounds (asymmetric alkylation) to prochiral aldehydes or ketones is currently one of the most important synthetic procedures to obtain chiral alcohols[1-3], which are natural biologically active compounds[4] and are also very useful synthetic precursors, as in the syntheses of some drugs and insecticides [5,6].

1,2 addition of dialkylzinc to aldehydes and ketones is extremely slow[7]. However, it is accelerated by substoichiometric amounts of such chiral substances as aminoalcohols and diols, including some carbohydrate derivatives[8,9]. In these conditions, a mixed catalyst is formed between Zn(II), the chiral ligand, and the carbonyl compound, which facilitates attack by the alkyl group (R-) on the prochiral carbonyl compound, preferentially on one of its faces.

After hydrolysis the alcohol is obtained, enriched in one configuration (R or S).

Recent studies have shown that when the ligand is a chiral diol with a Ti(IV) compound (for example $Ti(O^iPr)_4$), the reaction occurs in high yield and with high enantioselectivity[7-9].

The purpose of this paper was to study catalysis by the derivative of D-xylose **1** and $Ti(O^iPr)_4$ in the asymmetric alkylation of benzaldehyde with diethylzinc to obtain, after acid hydrolysis, 1-phenyl-1-propanol in high yield and with moderate enantioselectivity.

Results and Discussion

1,2 Enantioselective addition of diethylzinc to benzaldehyde catalyzed by an organometallic Ti(IV) compound and derivative **1**

We found that the **1** and Ti(IV) catalytic system acts optimally in the mixture of 0.1 mL (1 mmol) of anhydrous benzaldehyde and 3 mL (3 mmol) of Et_2Zn in 2.5 mL of anhydrous CH_2Cl_2 in a Schlenk tube under nitrogen at room temperature with constant stirring. Under these conditions, a sufficient amount of 1-phenyl-1-propanol was obtained for its characterization and quantification by gas chromatography (GC). From the area under the chromatogram peaks we determined the yield (conversion % of benzaldehyde into 1-phenyl-1-propanol) and the enantioselectivity (ee %) of the reactions (Tables 1 and 2) and the products were identified by ^{1}H-NMR. The predominant configuration was determined for each catalytic system[11, 12].

To optimize the concentration conditions of the catalytic system of **1** and Ti(IV), several reactions were carried out by using mixtures of **1** in variable substoichiometric amounts (2.5, 5.0, 10.0, and 20.0 mol %) with respect to benzaldehyde with 1 mmol of $Ti(O^iPr)_4$, because with concentrations of that order other authors[6,12] had achieved good results with other chiral catalysts and we had earlier obtained promising results with them[14,15].

A high conversion of benzaldehyde into 1-phenyl-1-propanol was obtained after a 6 h reaction, with Ti(IV) and 10.0 mol % of **1** with respect to benzaldehyde at room temperature (entry 8 in Table 1), indicating that the catalyst formed *in situ* in this reaction is effective with small amounts of **1** (Table 1). After an 18 h reaction, maximum conversion of benzaldehyde into 1-phenyl-1-propanol was obtained with 10.0 mol % of **1** (entry 12 in Table 1). After a 24 h reaction, there

was decreased conversion of benzaldehyde into 1-phenyl-1-propanol (entries 14 and 15 in Table 1), because of decomposition of 1-phenyl-propanol after 18 hours[11].

The optical rotation (α^o) of all the asymmetric alkylation products with **1** had a negative sign, (−), indicating that the 1-phenyl-1-propanol preferably has the S configuration (Tables 1 and 2)[13].

Enantioselectivity (45% ee) was achieved after a 6 h reaction with 10.0 mol % of **1** (entry 8 in Table 1). A larger amount of **1** (20%) did not increase enantioselectivity significantly (entry 9 in Table 1) probably because the sugar derivative **1** acts with Ti(IV) forming a chiral catalyst of the Ti(IV)-sugar type with an optimum amount of **1**, in this case 10.0 mol % of that derivative with respect to benzaldehyde.

Lowering the temperature from room temperature to 0° C and -20° C decreased conversion of benzaldehyde into 1-phenyl-1-propanol (Table 2), but the lower temperature did not significantly increase the enantioselectivity (ee %) of the reaction (Table 2). This is probably because the determining step in the asymmetric reaction is controlled by the structure of the metal-sugar type chiral catalyst, which should not depend very much on temperature[7, 8,11, 12].

The use of other solvents such as toluene or THF rather than CH_2Cl_2 produced no significant improvement in conversion or enantioselectivity (Table 2). Thus, most reactions were carried out in CH_2Cl_2[11].

In order to test the catalytic capacity of **1** with other metal ions, alkylation of benzaldehyde with $ZnEt_2$ was studied by using Co(II) or Cu(II). The reaction was carried out with Co(II) or Cu(II) acetylacetonate ($Co(acac)_2$ or $Cu(acac)_2$) (Table 2) instead of $Ti(O^iPr)_4$. Conditions for the reactions with these ions were the same as used with the Ti(IV) and **1** system. The catalytic system of Co(II) and **1** gave lower conversion and enantioselectivity of 1-phenyl-1-propanol than those achieved with Ti(IV) and **1** (Table 2). The Cu(II) and **1** system did not catalyze the reaction. These results indicate that the metal-sugar type catalyst in the asymmetric alkylation

must be an octahedral complex as obtained with Ti(IV) and Co(II), and not a square planar one formed mainly by Cu(II).

Therefore, optimum catalytic conditions in asymmetric alkylation are with 10 mol % of **1** with respect to benzaldehyde, and Ti(IV) as the metal reaction center in CH_2Cl_2 (entry 8 in Table 1)[11]. The conversion and enantioselectivity of the reaction in the presence of **1** and $Ti(O^iPr)_4$ probably involve formation of a complex of the "Ti(IV)-sugar" type, allowing ethyl group (Et-) transfer preferentially to one of the faces of benzaldehyde, and favoring formation of the enantiomer with the S configuration of the product.

The possible mechanism for asymmetric alkyl addition is given in Scheme 1. The reaction of the xylose derivative **1** with 1 molar equiv of $Ti(O^iPr)_4$ involves the dimeric complex **2,** because $Ti(O^iPr)_4$ reacts with **1** (1:1) in CH_2Cl_2, giving $\{[Ti(IV)(\mathbf{1})(O^iPr)_2]\cdot 2(CH_2Cl_2)\}_2$ (C 36.26 (36.80); H 5.48 (5.37); % found (% calculated)). Complex **2** further reacts with 1 molar equiv of $Ti(O^iPr)_4$, giving another dimeric complex, **3**. These dimeric complexes have been postulated in the literature on titanium catalysis of asymmetric alkylation[16-22,25]. Complex **3** reacts with Et_2Zn or with $EtTi(O^iPr)_3$, giving complex **4.** $EtTi(O^iPr)_3$ can be generated from reaction of excess $Ti(O^iPr)_4$ with Et_2Zn. as described for similar catalytic systems[7,25]. Complex **4** further reacts with 1 mole of benzaldehyde, giving complex **5**. To achieve the S configuration of the chiral alcohol, the attached Et- moves to the carbonyl carbon and the benzaldehyde oxygen probably moves simultaneously toward the second titanium center with the attached alkyl group, giving complex **6**. Complex **6** gives complex **2**. Regeneration of the starting complex **2** completes the catalytic cycle.

Conclusions

The presence of derivatives of D-xylose (**1**) in a substoichiometric amount with $Ti(O^iPr)_4$ in the asymmetric alkylation of benzaldehyde with Et_2Zn forms a chiral catalyst of dimeric complexes **6** ensuring the conversion and enantioselectivity of the reaction. The best catalytic condition (conversion and enantioselectivity) was achieved with 10.0 mol% of **1** with respect to benzaldehyde. The conversion and enantioselectivity achieved in the synthesis of the alcohol with **1** is due to the formation within the reaction system of dimeric complexes Ti(IV)-sugar (Scheme 1), facilitating transfer of the ethyl group to one face of benzaldehyde. The intrinsic chiral properties of carbohydrate **1** are transmitted through the dimeric Ti(IV)-sugar type complexes formed during the synthesis of 1-phenyl-1-propanol, yielding preferably its S enantiomer. The catalytic efficiency of the dimeric Ti(IV)-sugar complexes in the asymmetric alkylation of benzaldehyde with diethylzinc is determined by their stability and rigidity.

Experimental

All reagents and solvents were analytical grade.

Enantioselective 1,2-addition of diethylzinc to benzaldehyde catalyzed by a Ti(IV) organometallic compound and a xylose derivative

Compound **1** (19 mg, 10.0 mol % with respect to benzaldehyde) was placed in a dry 50 mL Schlenk tube, closed with a silicone stopper, and air was removed by purging three times with nitrogen and vacuum. The following were then added successively: 0.1 mL (1 mmol) benzaldehyde, 2.5 mL dichoromethane, 0.3 mL (1 mmol) 97% titanium(IV) isopropoxide, and finally 3 mL (3 mmol) of a 1-mol L^{-1} solution of Et_2Zn in hexane.

The reaction proceeded with stirring for 3 hours at room temperature, and was stopped by adding a saturated solution of ammonium chloride (releasing ethane and forming a white precipitate of

zinc oxide). The mixture was transferred to a separatory funnel, 10 mL of 2-mol L^{-1} HCl were added, and the product was extracted with three 10-mL portions of ethyl ether, dried with anhydrous $MgSO_4$ and the ether was evaporated, yielding crude 1-phenyl-1-propanol.

This general procedure was applied to all the catalytic reactions with different concentrations, solvents and reaction temperatures as shown in Tables 1 and 2 under Results and Discussion.

Product Analysis.

To analyze the products and determine percentage conversion, the sample, 0.4 μL, was injected into an HP 5890 series II gas chromatograph equipped with an Allchrom plus program and a methylsilicone-gum-type 5 m x 0.53 mm x 2.65 μm column. Working conditions were:

Initial temperature, 100 °C; initial time, 5 min; rate, 20 °C/min; final time, 18 min; pressure, 10 psi.

t_R(benzaldehyde) = 7.8 min t_R(1-phenyl-1-propanol) = 11.9 min

The percentage conversion was determined from the peak areas of products and unreacted benzaldehyde by:

$$\% \text{ conversion} = \frac{\text{1-phenyl-1-propanol area}}{\text{(1-phenyl-1propanol area + benzaldehyde area)}} \times 100$$

Conversion percentages were confirmed by ^{1}H-NMR spectroscopy. The products were dissolved in $CDCl_3$ and run on a Bruker DRX-300 spectrometer at 300 MHz. Calculation of conversion % was made from the areas of the Ph–C**H**(Et)-OH proton signal of 1-phenyl-1-propanol located at 4.5 ppm and that of the C**H**O of benzaldehyde located at 10.0 ppm with respect to TMS.

The enantiomeric excess (ee %) was estimated on an HP 5890 series II gas chromatograph with an Allchrom plus program and a Supelco β-Dex 120 30 m x 0.25 mm x 0.25 μm chiral capillary column at:

Initial temperature, 100 °C; initial time, 10 min; rate, 1 °C/min; pressure, 10 psi. Retention times were the following:

t_R (S-1-phenyl-1-propanol) = 28.7 min t_R (R-1-phenyl-1-propanol) = 29.7 min

The ee % was calculated from the corresponding areas of the signals of the S and R enantiomers of 1-phenyl-1-propanol:

$$\%\ ee = \left| \frac{\text{S-1-phenyl-1-propanol area} - \text{R-1-phenyl-1-propanol area}}{(\text{S-1-phenyl-1-propanol area} + \text{R-1-phenyl-1-propanol area})} \right| x100$$

The predominant configuration of the products was given by the sign of the optical rotation measured at 20 ºC on a Perkin Elmer PE 241 polarimeter with the literature data [10]:

$[\alpha^o]_D$ (S-1-phenyl-1-propanol)= +48° at 20 ºC and $[\alpha^o]_D$ (R-1-phenyl-1-propanol)= –48° at 20 °C.

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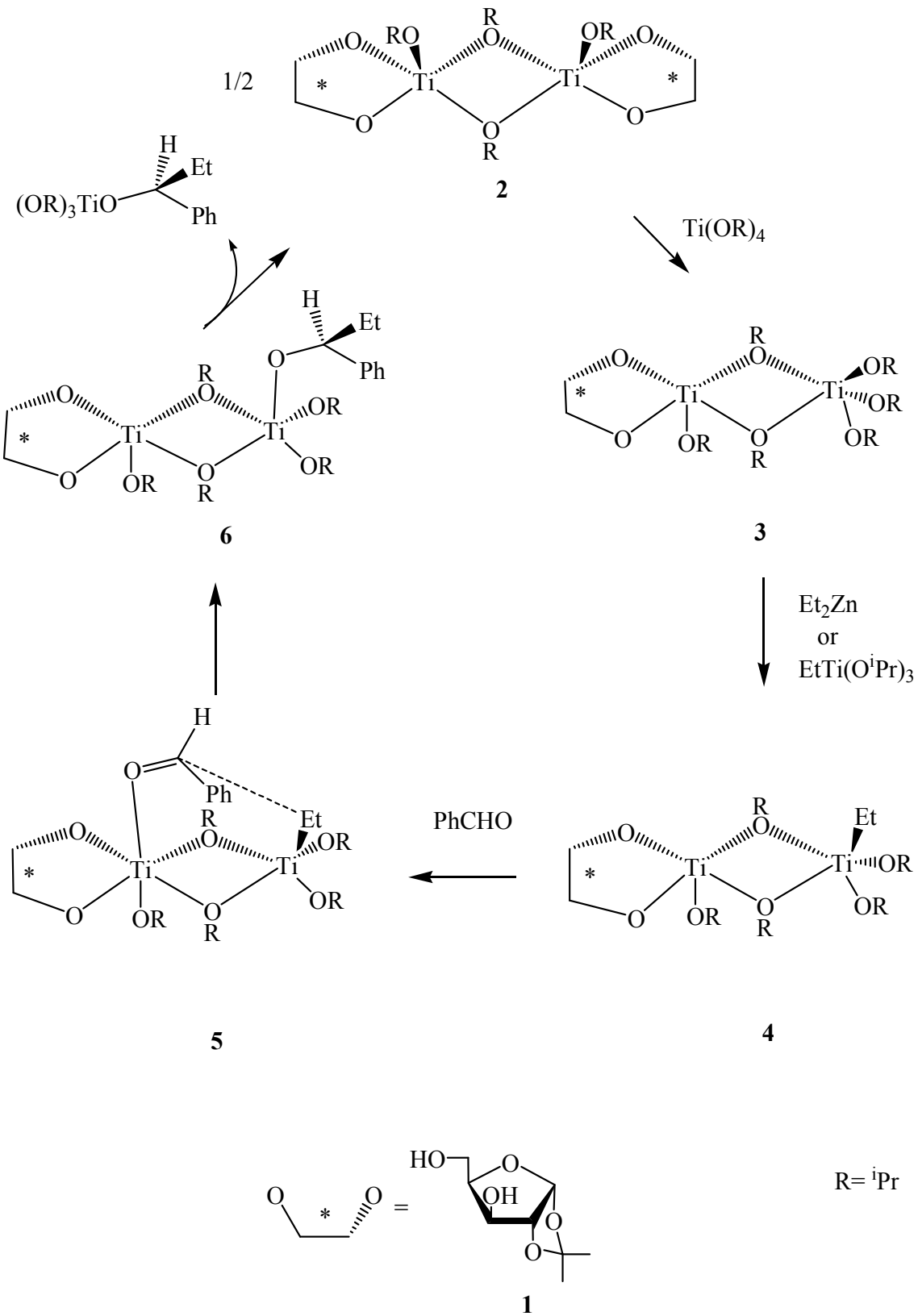


Scheme 1

Table 1

Asymmetric alkylation of benzaldehyde with Et_2Zn catalyzed by carbohydrate derivative **1** and $Ti(O^iPr)_4$.[a)]

Entry	*Percentage Conversion* [c)]	% ee [d)] (Confign.)[e)]	*mol % of 1* [b)]	*Reaction time (hr)*
1	15	2(S)	0	3
2	55	17(S)	2.5	3
3	60	20(S)	5.0	3
4	80	33(S)	10.0	3
5	83	31(S)	20.0	3
6	53	20(S)	2.5	6
7	63	30(S)	5.0	6
8	**85**	**45(S)**	**10.0**	**6**
9	80	48(S)	20.0	6
10	50	10(S)	2.5	18
11	45	20(S)	5.0	18
12	90	17(S)	10.0	18
13	29	26(S)	20.0	18
14	63	40(S)	10.0	24
15	70	33(S)	20.0	24

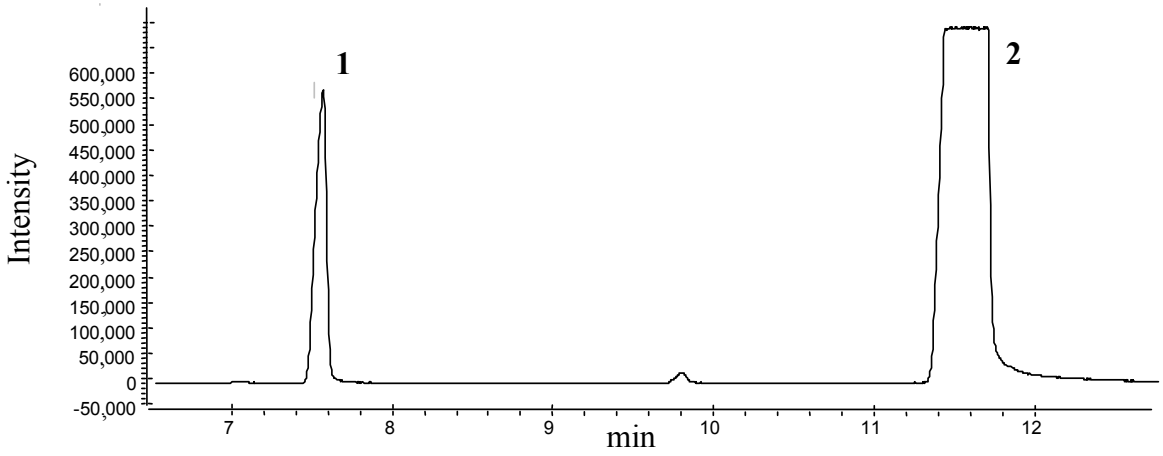
[a)] Reaction with 1 mmol of benzaldehyde and 3 mmol of Et_2Zn in the presence of 1 mmol of $Ti(OiPr)_4$. [b)] Mol percentages referred to benzaldehyde. [c)] Determined by GC [d)] Determined by GC. with β-DEX 120 column. [e)] Determined from optical rotation.

Table 2

Results of the asymmetric alkylation of benzaldehyde with Et_2Zn catalyzed by carbohydrate derivative **1** and a metal ion after 6 hr of reaction.[a), b)]

Entry	Porcentage conversion[c)]	% ee [d)] (confign.)[e)]	Metal center	Solvent	Temperature (ºC)
1 [a)]	43	15(S)	Ti(IV) [a)]	CH_2Cl_2	-20
2 [a)]	35	40(S)	Ti(IV) [a)]	CH_2Cl_2	0
3 [a)]	63	30(S)	Ti(IV) [a)]	CH_2Cl_2	20
1 [b)]	43	50(S)	Ti(IV) [b)]	CH_2Cl_2	-20
2 [b)]	70	40(S)	Ti(IV) [b)]	CH_2Cl_2	0
3 [b)]	**85**	**45(S)**	**Ti(IV)** [b)]	**CH_2Cl_2**	**20**
4 [b)]	66	35(S)	Ti(IV) [b)]	THF	20
5 [b)]	90	50(S)	Ti(IV) [b)]	Toluene	20
6	70	17(S)	Co(II) [b)]	CH_2Cl_2	20
7	13	3(S)	Cu(II) [b) b)]	CH_2Cl_2	20

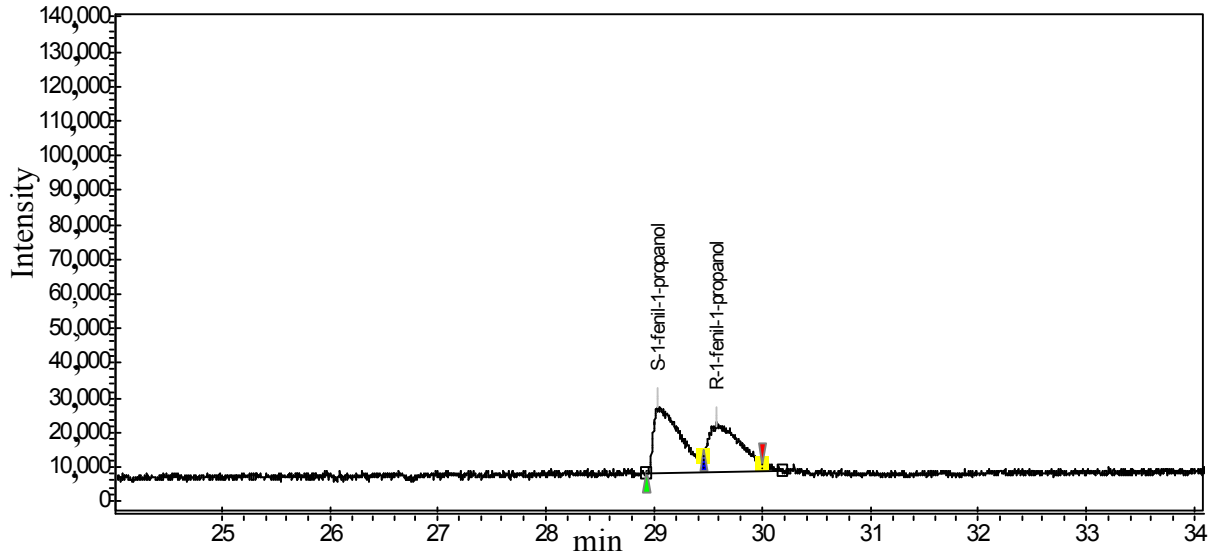
Reaction with [a)] 5.0 and [b)]10.0 mol % of **1** with respect to 1 mmol de benzaldehyde and 3 mmol Et_2Zn in the presence of 1 mmol of metal ion [c)] Determined by GC. [d)] Determined by GC with β-DEX 120 column. [e)] Determined from optical rotation.



#	Name	Time [min]	Area [%]
1	Benzaldehyde	7.53	17.0
2	1-phenyl-1-propanol	11.44	83.0
Total			100.0

% conversion = [83.0 / (17.0 + 83.0)] x 100 = 83%

Fig. 1 Chromatogram in column *Methyl silicone gum* 5m x 0.53mm x 2.65 μm of the asymmetric alkylation of benzaldehyde with Et_2Zn in the presence of 10.0 mol % of **1**. Entry 5, Table 1. Conditions in which the chromatogram was performed: Injector: temperature, 250 ºC; detector temperature, 250 ºC; pressure, 10 psi; initial temperature, 100 ºC; initial time, 5 min; rate, 20 ºC/min; final temperature, 180 ºC; final time, 18 min (top). Retention times (min) and peak areas of benzaldehyde and S- and R-1-phenyl-1-propanol present in the chromatogram are tabulated. Calculation of conversion % from these areas is shown at the bottom.



#	Name	Time [min]	Area [%]
1	S-1-phenyl-1-propanol	29.04	65.5
2	R-1-phenyl-1-propanol	29.59	34.5
Total			100.00

% ee = | (65.5 – 34.5) / (65.5 + 34.5) | x 100 = 31 % (S).

Fig. 2 Chromatogram in column *Supelco β-Dex 120* de 30m x 0,25mm x 0,25 μm of the asymmetric alkylation of benzaldehyde with Et_2Zn in the presence of 10.0 mol % of **1**. Entry 5, Table 1. Conditions in which the chromatogram was performed: Injector temperature, 250 ºC; detector temperature, 250 ºC; pressure, 10 psi; initial temperature, 100 ºC; initial time, 10 min; rate, 1 ºC/min; final temperature, 140 ºC; final time, 4 min (top). Retention times (min) and peak areas of benzaldehyde and S- and R-1-phenyl-1-propanol present in the chromatogram are tabulated. Calculation of ee % from these areas is shown at the bottom.