

Enantioselective Addition of Diethylzinc to Benzaldehyde Catalyzed by an Organometallic Ti(IV) Compound and a Xylose Derivative

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Um derivado da D-xylose, 1,2-O-isopropilideno- α -D-xilofuranose (**1**), com $\text{Ti}(\text{O}^i\text{Pr})_4$ foi usado como catalisador quiral na alquilação assimétrica do benzaldeído com dietilzinco (Et_2Zn) para produção de 1-fenil-1-propanol em alto rendimento (conversão de 90%) e enantiosseletividade moderada (45% *ee* (*S*)). As condições ótimas (conversão e enantiosseletividade) para o sistema catalítico formado por **1** e Ti(IV) foram 10.0 mol % de **1** e 1 equivalente de Ti(IV) com relação ao benzaldeído em CH_2Cl_2 como solvente, a temperatura ambiente. Na alquilação assimétrica do benzaldeído com Et_2Zn , o composto **1** em quantidade sub-estequiométrica com $\text{Ti}(\text{O}^i\text{Pr})_4$ forma um catalisador quiral do tipo Ti(IV)-açúcar, o que assegura uma conversão com bom rendimento e a enantiosseletividade da reação.

A derivative of D-xylose, 1,2-O-isopropylidene- α -D-xylofuranose (**1**), with $\text{Ti}(\text{O}^i\text{Pr})_4$ 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 $\text{Ti}(\text{O}^i\text{Pr})_4$ 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 compounds⁴ 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 $\text{Ti}(\text{O}^i\text{Pr})_4$), 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 $\text{Ti}(\text{O}^i\text{Pr})_4$ 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

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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 $^1\text{H-NMR}$. 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 $\text{Ti}(\text{O}^i\text{Pr})_4$, 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°) 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**,

Table 1. Asymmetric alkylation of benzaldehyde with Et_2Zn catalyzed by carbohydrate derivative **1** and $\text{Ti}(\text{O}^i\text{Pr})_4$ ^a

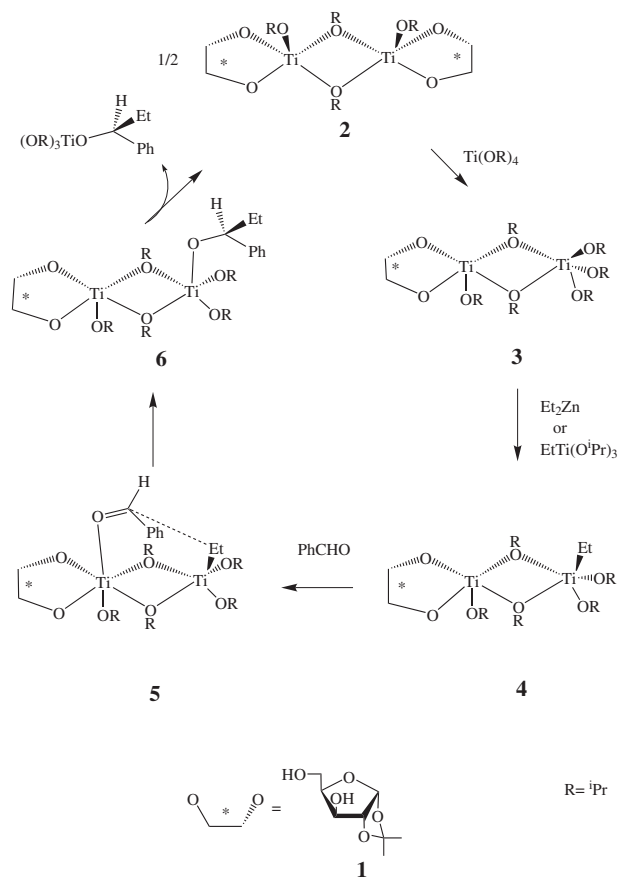
Entry	Percentage Conversion ^c	% <i>ee</i> ^d (Config.) ^e	mol% of 1 ^b	Reaction time / h
1	15	2(<i>S</i>)	0	3
2	55	17(<i>S</i>)	2.5	3
3	60	20(<i>S</i>)	5.0	3
4	80	33(<i>S</i>)	10.0	3
5	83	31(<i>S</i>)	20.0	3
6	53	20(<i>S</i>)	2.5	6
7	63	30(<i>S</i>)	5.0	6
8	85	45(<i>S</i>)	10.0	6
9	80	48(<i>S</i>)	20.0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

^aReaction with 1 mmol of benzaldehyde and 3 mmol of Et_2Zn in the presence of 1 mmol of $\text{Ti}(\text{O}^i\text{Pr})_4$. ^bMol percentages referred to benzaldehyde. ^cDetermined by GC. ^dDetermined by GC with β -DEX 120 column. ^eDetermined from optical rotation.

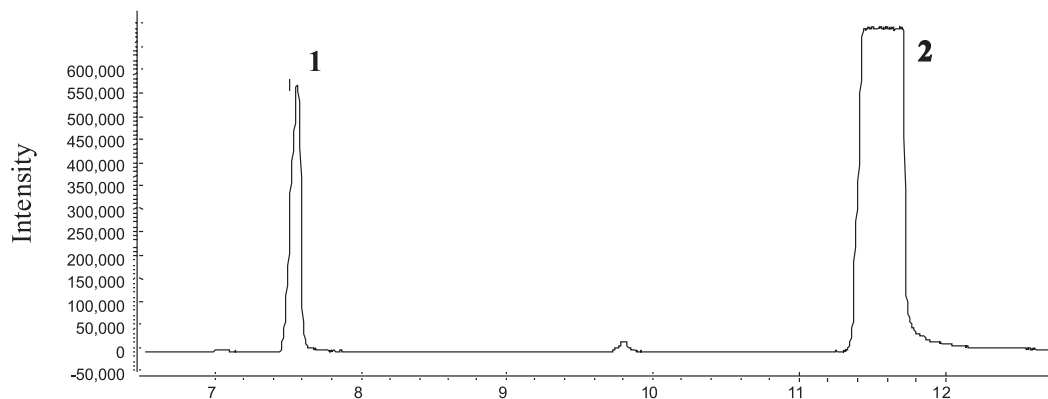
Table 2. Results of the asymmetric alkylation of benzaldehyde with Et_2Zn catalyzed by carbohydrate derivative **1** and a metal ion after 6 h of reaction^{a,b}

Entry	Percentage conversion ^c	<i>ee%</i> ^d (config.) ^e	Metal center	Solvent	T / °C
1 ^a	43	15(<i>S</i>)	Ti(IV) ^a	CH_2Cl_2	-20
2 ^a	35	40(<i>S</i>)	Ti(IV) ^a	CH_2Cl_2	0
3 ^a	63	30(<i>S</i>)	Ti(IV) ^a	CH_2Cl_2	20
1 ^b	43	50(<i>S</i>)	Ti(IV) ^b	CH_2Cl_2	-20
2 ^b	70	40(<i>S</i>)	Ti(IV) ^b	CH_2Cl_2	0
3 ^b	85	45(<i>S</i>)	Ti(IV) ^b	CH_2Cl_2	20
4 ^b	66	35(<i>S</i>)	Ti(IV) ^b	THF	20
5 ^b	90	50(<i>S</i>)	Ti(IV) ^b	Toluene	20
6	70	17(<i>S</i>)	Co(II) ^b	CH_2Cl_2	20
7	13	3(<i>S</i>)	Cu(II) ^b	CH_2Cl_2	20

Reaction with ^a5.0 and ^b10.0 mol% of **1** with respect to 1 mmol de benzaldehyde and 3 mmol Et_2Zn in the presence of 1 mmol of metal ion^cdetermined by GC. ^dDetermined by GC with β -DEX 120 column. ^eDetermined from optical rotation.



Scheme 1.



Peak	Compound	time / min	Area / (%)
1	Benzaldehyde	7.53	17.0
2	1-phenyl-1-propanol	11.44	83.0
Total			100.0

$$\text{conversion \%} = [83.0 / (17.0 + 83.0)] \times 100 = 83\%$$

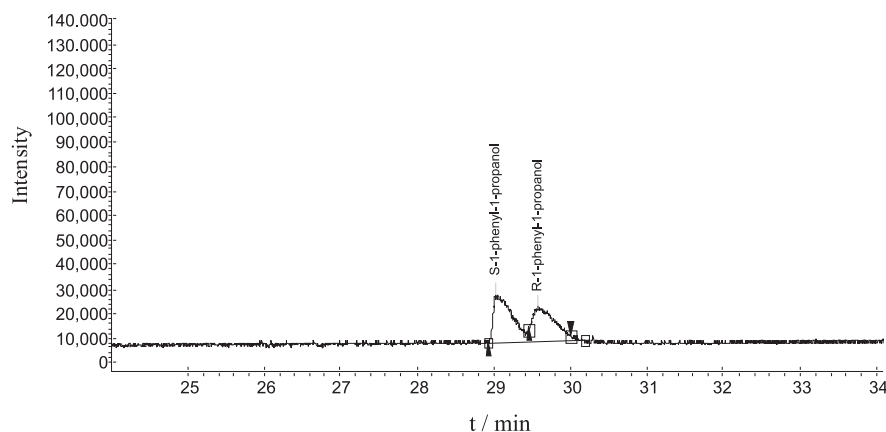
Figure 1. Chromatogram in column methyl silicone gum 5m × 0.53mm × 2.65 μm of the asymmetric alkylation of benzaldehyde with Et₂Zn in the presence of 10.0 mol% of **1**. Entry 5, Table 1. Conditions in which the chromatogram was performed: Injector temperature, 250 °C; detector temperature, 250 °C; pressure, 10 psi; initial temperature, 100 °C; initial time, 5 min; rate, 20 °C min⁻¹; final temperature, 180 °C; 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.

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 CH₂Cl₂ produced no significant improvement in conversion or enantioselectivity (Table 2). Thus, most reactions were carried out in CH₂Cl₂.¹¹

In order to test the catalytic capacity of **1** with other metal ions, alkylation of benzaldehyde with ZnEt₂ 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(OⁱPr)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



Peak	Compound	time / min	Area / (%)
1	<i>S</i> -1-phenyl-1-propanol	29.04	65.5
2	<i>R</i> -1-phenyl-1-propanol	29.59	34.5
Total			100.00

$$ee\% = [(65.5 - 34.5) / (65.5 + 34.5)] \times 100 = 31\% (S)$$

Figure 2. Chromatogram in column Supelco β -Dex 120 de 30 m \times 0.25 mm \times 0.25 μ m 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 $^\circ\text{C}$; detector temperature, 250 $^\circ\text{C}$; pressure, 10 psi; initial temperature, 100 $^\circ\text{C}$; initial time, 10 min; rate, 1 $^\circ\text{C min}^{-1}$; final temperature, 140 $^\circ\text{C}$; 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.

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 $\text{Ti}(\text{O}^i\text{Pr})_4$ 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 $\text{Ti}(\text{O}^i\text{Pr})_4$ involves the dimeric complex **2**, because $\text{Ti}(\text{O}^i\text{Pr})_4$ reacts with **1** (1:1) in CH_2Cl_2 , giving $\{[\text{Ti}(\text{IV})(\text{1})(\text{O}^i\text{Pr})_2] \cdot 2(\text{CH}_2\text{Cl}_2)\}_2$ (C 36.26 (36.80); H 5.48 (5.37); %found (%calculated)). Complex **2** further reacts with 1 molar equiv. of $\text{Ti}(\text{O}^i\text{Pr})_4$, 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 $\text{EtTi}(\text{O}^i\text{Pr})_3$, giving complex **4**. $\text{EtTi}(\text{O}^i\text{Pr})_3$ can be generated from reaction of excess $\text{Ti}(\text{O}^i\text{Pr})_4$ with Et_2Zn , as described for similar catalytic systems.^{7,25} Complex **4** further reacts with 1 mol 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 $\text{Ti}(\text{O}^i\text{Pr})_4$ 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 dichloromethane, 0.3 mL (1 mmol) 97% titanium(IV) isopropoxide, and finally 3 mL (3 mmol) of a 1 mol L⁻¹ solution of Et₂Zn 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 MgSO₄ 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 × 0.53 mm × 2.65 μm column. Working conditions were:

Initial temperature, 100 °C; initial time, 5 min; rate, 20 °C min⁻¹; final time, 18 min; pressure, 10 psi.

Retention times were: t_R(benzaldehyde) = 7.8 min and t_R(1-phenyl-1-propanol) = 11.9 min. The percentage conversion was determined from the peak areas of products and unreacted benzaldehyde by: % conversion = [(1-phenyl-1-propanol area) / (1-phenyl-1-propanol area + benzaldehyde area)] × 100.

Conversion percentages were confirmed by ¹H-NMR spectroscopy. The products were dissolved in CDCl₃ and

run on a Bruker DRX-300 spectrometer at 300 MHz. Calculation of conversion% was made from the areas of the Ph-CH(Et)-OH proton signal of 1-phenyl-1-propanol located at 4.5 ppm and that of the CHO 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 × 0.25 mm × 0.25 μm chiral capillary column at initial temperature, 100 °C; initial time, 10 min; rate, 1 °C min⁻¹; 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*% = | *S*-1-phenyl-1-propanol area – *R*-1-phenyl-1-propanol area | / (*S*-1-phenyl-1-propanol area + *R*-1-phenyl-1-propanol area) × 100.

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

[α_D²⁰]_D (*S*-1-phenyl-1-propanol) = +48° at 20 °C and [α_D²⁰]_D (*R*-1-phenyl-1-propanol) = –48° at 20 °C.

Acknowledgments

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