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Enantioselective ethylation of aromatic aldehydes catalysed by titanium(IV)–*bis*-BINOLate-2′,2″-propylether complexes: An inside view of the catalytic active species

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ABSTRACT

A series of *bis*-BINOL-2′,2″-propyl ethers with different substituents at the propyl ether bridge, were investigated in the asymmetric titanium catalysed ethylation of arylaldehydes with Et_2Zn, with conversions up to 99% and enantiomeric excesses up to 80%. Semiempirical PM6 calculations indicate that the higher ability of the unsubstituted ligand to form chelated titanium complexes could be related to its higher enantioselectivity. Catalytic experiments with partially optically enriched ligand put in evidence a negative non-linear effect (−)-NLE that suggest the presence of two ligand molecule in the active titanium species. Further catalytic data, together with ^{1}H NMR and circular dichroism (CD) titrations of the ligand with $Ti(^iPrO)_4$, as well as ESI-MS experiments, allow to propose a trinuclear species $[Ti_3L_2(O^iPr)_8]$ (L = dianion of (1*R*,1′*R*)-2′,2″-(propane-1,3-diyl)*bis*(oxy)di-1,1′-binaphthyl-2-ol) as responsible for the catalytic asymmetric addition of Et_2Zn to aldehydes. This catalytic species is only formed with great $Ti(O^iPr)_4$/ligand molar ratios (*ca.* 8).

1. Introduction

The enantioselective addition of organometallic reagents to aldehydes affords optically active secondary alcohols. This is a very important reaction in organic synthesis, since chiral secondary alcohols are components of many naturally occurring biologically active compounds. These alcohols are also valuable intermediates for the synthesis of other functionalities, such as halides, amides, esters, and ethers [1].

In recent years, the enantioselective addition of organozinc reagents to aldehydes has been extensively studied [2]. Numerous catalytic systems have been developed for this reaction, often providing excellent enantioselectivities [3].

Among the countless examples of metal complexes of BINOL as asymmetric catalysts, a key role is played by the Ti(IV) complexes family. In spite of their synthetic importance, there is little information regarding the structure of these titanium complexes [4]. Only [BINOLate)$Ti(O^iPr)_2$] and its derivatives are relatively well characterized. However, the structure in solution of these complexes is difficult to establish owing to the kinetic lability of titanium alkoxide ligands [5]. However, the structure in solution of these complexes is difficult to establish owing to the kinetic lability of titanium alkoxide ligands. Moreover, the characterization of active catalysts is hampered by aggregation phenomena [6].

Catalysts containing partially hydrogenated BINOL ligands, 5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-bi-2-naphthol (H_8-BINOL) [7], and 5,6,7,8-tetrahydro-1,1′-bi-2-naphthol (H_4-BINOL) [8], exhibited in some cases better stereoselectivity than those obtained from the corresponding BINOL catalysts [9]. This has been attributed to the steric and electronic modulation produced by the saturated fragment in the binaphthyl backbone [10].

It is well known that the accurate identification of the nature and structure of enantioselective catalysts or catalytic precursors is always a significant piece of information, since it may open the way to the rational design of new and more efficient chiral auxiliaries. In some special cases, the structural elucidation of the catalytic species represents itself an important task from the spectroscopic point of view.

We have recently reported the synthesis of a series of *bis*-BINOL-2′,2″-ether ligands and their catalytic evaluation in the enantioselective ethylation of benzaldehyde. Among the *bis*-BINOL-2′,2″-ethers tested, those containing a propyl ether bridge showed the best performance [11]. Herein we report the effect of the substituents on the propyl ether bridge on the activity and

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selectivity of catalytic ethylation of aromatic aldehydes. It should also be pointed out that this paper describes the first insight into the mechanistic studies of catalytic alkylation of aldehydes using *bis*-BINOLate–Ti complexes. So, an insight view of the catalytic active species is described, using several approaches, including detailed analysis of the catalytic data, spectroscopic characterization by ^{1}H NMR, circular dichroism (CD) and ESI-MS of solution samples.

2. Experimental

2.1. General

All catalytic and synthetic reactions were performed using standard Schlenk techniques, under N_2 inert atmosphere. Glassware was oven-dried. Solvents were purified by standard procedure and reagents were used as received. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ solution on Bruker 250, 300 or 400 spectrometers. Chemical shifts are relative to $SiMe_4$. Circular dichroism (CD) measurements were gathered with a JASCO model J-715 spectrophotometer equipped with a computer (J-700 software, JASCO). These measurements were carried out at a constant temperature (25 °C) maintained by a Peltier PTC-351 apparatus (TE Technology Inc., Traverse City, MI, USA). A high resolution ESI mass spectrometer Bruker microTOFQ was used to characterize the new ligands. Medium resolution spectra of catalytic solutions, prepared dissolving Ti(O^iPr)$_4$ plus ligand in CH_2Cl_2/Pr^iOH (10/1) were recorded on a Brucker Squire 3000 equipped with an ESI source. Conversion and chemoselectivity were obtained by gas chromatography on an Agilent-6890, equipped with a capillary HP5 column (30 m × 0.32 mm i.d., 0.25 μm film thickness, carrier gas N_2, F.I.D. detector). The enantiomeric excesses and absolute configuration were measured with Konik-300C gas chromatograph equipped with β-cyclodextrin capillary column (Supelco β-Dex120, 30 m × 0.25 mm). The configuration of the alcohols was determined by comparison with optically pure samples of (*R*) and (*S*)-2-phenyl-2-propanol.

2.2. Ligand synthesis

(1*R*,1″*R*)-2′,2″-(2*R*,4*R*)-pentane-2,4-diyl*bis*(oxy)di-1,1′-binaphthyl-2-ol **1** (1*S*,1″*S*)-2′,2″-(2*R*,4*R*)-pentane-2,4-diyl*bis*(oxy)di-1,1′-binaphthyl **2**, were prepared according to previously described procedure, and all the analytical data are in good agreement with previously reported [12].

2.2.1. General procedure for the synthesis of ligands bis-BINOL-2′,2″-propyl ether and derivatives 3–5

(i) (*R*)-2′-(benzyloxy)-1,1′-binaphthyl-2-ol (*R*)-BnBINOL: The compound was synthesized by slightly modified Mitsunobu reaction [11–13]. To a stirred solution of (*R*)-binaphthol (5.0 g, 17.5 mmol), PPh_3 (4.59 g, 17.5 mmol) and benzyl alcohol (2.1 mL, 20 mmol) in dry THF (200 mL), a solution of diethyl azodicarboxylate (DEAD) (7.7 mL, 40% in toluene, 17.5 mmol) was added dropwise. The reaction was kept with stirring at room temperature during 48 h. Then, the mixture was evaporated under reduced pressure. The residue was redissolved in dichloromethane and washed with water and brine. After partial evaporation of the solvent at reduced pressure, the residue was purified by preparative chromatography (silica, CH_2Cl_2:*n*-hexane, 1:1). After evaporation of solvents, the solid was recrystallized from toluene/*n*-hexane, to afford 5.73 g (87% yield) of the product as white solid. Physical and spectroscopic data were in agreement with the literature data [12].

(ii) To a suspension of sodium hydride (160 mg, 60% in paraffin, 4 mmol) in dry dimethylformamide (DMF) (10 mL, 0 °C), a solution of (*R*)-2′-(benzyloxy)-1,1′-binaphthyl-2-ol (2.7 mmol) in dry DMF (5 mL) was added dropwise along 30 min. A solution of the desired alkane ditosylate (1.3 mmol) in dry DMF was then slowly added to the previous mixture (0 °C, 1 h). After the addition of ditosylalkane was completed, the reaction was stirred for 6 h at 80 °C. After cooling the reaction mixture, water was added dropwise (0 °C) and the organic compound was extracted with CH_2Cl_2. The organic layer was washed with water and a brine solution, and the concentrated organic phase was purified by flash chromatography (silica, CH_2Cl_2/*n*-hexane 2:1). The crude was recrystallized from AcOEt/Pr^iOH.

1,3-*bis*[(*R*)-2′-(benzyloxy)-1,1′-binaphthyl-2-yloxy]propane **5a** was obtained with 85% yield and data is in agreement with our previously described procedure [11].

(1*R*,1″*R*)-2′,2″-(2,2-dimethylpropane-1,3-diyl)*bis*(oxy)*bis*(2-(benzyloxy)-1,1′-binaphthyl **3a**, was obtained in 85% yield, as a white powder. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (dd, J = 14.3, 6.4 Hz, 8H), 7.40–7.15 (m, 10H), 7.13–6.92 (m, 10H), 6.82 (d, J = 8.7 Hz, 16H), 4.81 (m, 4H), 3.19 (d, J = 8.3 Hz, 2H), 3.05 (d, J = 8.3 Hz, 2H), 0.18 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.09, 154.00, 137.73, 134.27, 134.06, 129.38, 129.11, 129.03, 128.11, 127.90, 127.71, 127.23, 126.66, 126.22, 126.20, 125.55, 125.45, 123.77, 123.32, 121.09, 119.41, 116.10, 114.59, 73.45, 71.21, 35.71, 21.18; MS (ESI): m/z = 843.3411 (M+Na), calcd. for $C_{59}H_{48}O_4Na^+$ 843.3445.

(iii) A BBr_3 solution (1 M in CH_2Cl_2, 1.55 mL), was added to a dry CH_2Cl_2 solution of **3a** or **5a** (0.94 mmol, 10 mL) cooled at −78 °C and the reaction was stirred for 2 h at this temperature. When the mixture reached room temperature, the organic phase was washed with 2 M HCl(aq), and then dried over $MgSO_4$. The crude obtained by evaporation was purified by flash chromatography (silica, CH_2Cl_2). The compounds were recrystallized from toluene/*n*-hexane.

(1*R*,1′*R*)-2′,2″-(propane-1,3-diyl*bis*(oxy))di-1,1′-binaphthyl-2-ol) **5**, obtained with 78% yield and data is in agreement with our previously described procedure [11].

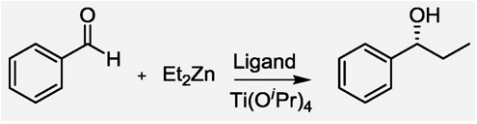
(1*R*,1″*R*)-2′,2″-(2,2-dimethylpropane-1,3-diyl)*bis*(oxy)di-1,1′-binaphthyl-2-ol **3** was obtained in 87% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06–7.75 (m, 8H), 7.35 (t, J = 7.3 Hz, 2H), 7.29–7.07 (m, 10H), 6.97 (m, 6H), 4.76 (s, 2H), 3.22 (d, J = 8.2 Hz, 2H), 3.14 (d, J = 8.2 Hz, 2H), 0.32 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.01, 151.04, 133.82, 130.70, 129.37, 129.19, 128.93, 128.16, 127.83, 127.11, 126.19, 124.90, 124.71, 123.89, 123.11, 117.33, 115.29, 114.99, 114.39, 35.58, 21.20. m.p. 101–102 °C. MS (ESI): m/z = 663.2482 (M+Na), calcd. for $C_{45}H_{36}O_4Na^+$ 663.2506.

(iv) A solution of **5a** (1.88 mmol) in $CHCl_3$/MeOH (3:1) in the presence of Pd/C 5% was submitted to 35 bar of H_2 along 72 h at the temperature of 35 °C. The reaction mixture was filtrated in celite, and the residue washed with methanol. Then, the mixture was evaporated under reduced pressure and the residue was purified by silica gel column chromatography using dichloromethane as eluent. The desired fraction was evaporated yielding (1*R*,1″*R*)-2′,2″-(propane-1,3-diyl*bis*(oxy))*bis*(5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-binaphthyl-2-ol) as a white powder. Yield (80%). Physical and spectroscopic data were in agreement with the literature data [11].

2.3. General procedure for the catalytic reactions

Titanium tetraisopropoxide (120 μL, 0.40 mmol) was added *via* syringe to the desired *bis*-BINOL-2′,2″-ethers (5.0×10^{-2} mmol) in the appropriate freshly dried solvent (2 mL), under N_2 atmosphere (15 min). To the resulting solution, diethylzinc (0.75 mL, 1.0 M in hexane, 0.75 mmol) was added, followed by the addition of arylic aldehyde (0.25 mmol). The reaction was kept at the appropriate temperature for 5 h and quenched by adding with 2 M HCl(aq). The aqueous layer was extracted with ethyl acetate and organic phase was then evaporated. The crude was redissolved in pentane, producing the precipitation of the ligand, which was removed

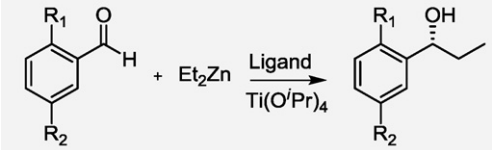
Table 1
Asymmetric ethylation of benzaldehyde **6** with Et_2Zn catalysed by $Ti(O^iPr)_4$ and *bis*-BINOL-2′,2″-ether ligands.[a]



Entry	Ligand	*T* (°C)	Conv.[b] (%)	*ee*[b] (%)
1	**1**	0	82	53 (*R*)
2	**2**		87	30 (S)
3	**3**		83	38 (*R*)
4	**4**		97	81 (*R*)
5	**5**	0	99	62 (*R*)
6		−10	70	55 (*R*)
7		40	99	47 (*R*)
8	–	0	75	–

[a] Reaction conditions: 0.25 mmol of benzaldehyde, 0.05 mmol of ligand, 0.75 mmol of Et_2Zn and 0.4 mmol of $Ti(O^iPr)_4$ in 2 mL of toluene.
[b] Conversion in 1-phenylpropanol and steroselectivity after 5 h reaction.

Table 2
Asymmetric addition of diethylzinc to aromatic aldehydes using $Ti(O^iPr)_4$ in the presence of ligands **4** and **5**.[a]



6: $R_1 = R_2 = H$
7: $R_1 = Cl$; $R_2 = H$
8: $R_1 = H$; $R_2 = Cl$

Entry	Subs.	Ligand	Solv.	conv.[b] (%)	*ee*[c] (%)
1	**6**	**4**	PhMe	97	81
2	**6**	**5**		99	62
3	**6**	**4**	DCM	62	80
4	**6**	**5**		93	69
5	**7**	**4**	PhMe	98	63
6	**7**	**5**		98	45
7	**7**	**4**	DCM	68	54
8	**7**	**5**		86	46
9	**8**	**4**	PhMe	80	79
10	**8**	**5**		99	68
11	**8**	**4**	DCM	71	80
12	**8**	**5**		85	65

[a] Reaction conditions: 0.25 mmol of aryldehyde, 0.05 mmol of ligand, 0.75 mmol of Et_2Zn and 0.4 mol of $Ti(O^iPr)_4$ in 2 mL of toluene.
[b] % of conversion in alcohol after 5 h reaction.
[c] % of enantiomeric excess in (*R*)-1-arylpropan-1-ol.

by filtration. The resulting solution was analyzed by GC, GC/MS and GC equipped with a chiral column. The data are collected in Tables 1 and 2.

3. Results and discussion

3.1. Ligand synthesis

In our previous work, we showed that *bis*-BINOL-2′,2″-propyl ether **5** was one of the most active and selective ligand in asymmetric titanium catalysed ethylation of benzaldehyde [11]. In an attempt to improve the catalytic performance of *bis*-BINOLate-2′,2″-propyl ether titanium(IV) complexes we enlarge these studies investigating the behavior of ligands **1**–**3**, Scheme 1. Ligands **1** and **2**, incorporate methyl substituents on the propyl fragment, leading to two additional stereogenic centers, while with ligand **3** the methyl groups only add steric hindrance to the bridge. Results with ligands **4** and **5** are reported for comparative purposes.

Ligands **1**, **2**,**4** and **5** were prepared accordingly to previously described methods [11,12].

Ligand **3** was synthesized using our previously synthetic strategy [11]. Firstly (*R*)-BnBINOL was prepared from the reaction of BINOL with benzyl alcohol *via* slightly modifications of Mitsunobu reaction. The (*R*)-BnBINOL was coupled with 2,2-dimethylpropane-1,3-diyl-*bis*(4-methylbenzenesulfonate) affording (1*R*,1″*R*)-2′,2″-(2,2-dimethylpropane-1,3-diyl)*bis*(oxy)*bis*(2-(benzyloxy)-1,1′-binaphthyl) **3a** in 85% yield, followed by BBr_3 benzyl deprotection. In this way (1′*R*,1′*R*)-2′,2″-(2,2-dimethylpropane-1,3-diyl)*bis*(oxi)di-1,1′-bibenzobenzen-2-ol **3** was obtained in 87% yield, after chromatographic purification.

3.2. Catalytic asymmetric ethylation of aldehydes

Firstly, the performance of the ligands *bis*-BINOL-2′,2″-ethers **1**–**5**, on the titanium(IV) catalytic ethylation of benzaldehyde, was studied and the results are summarized in Table 1.

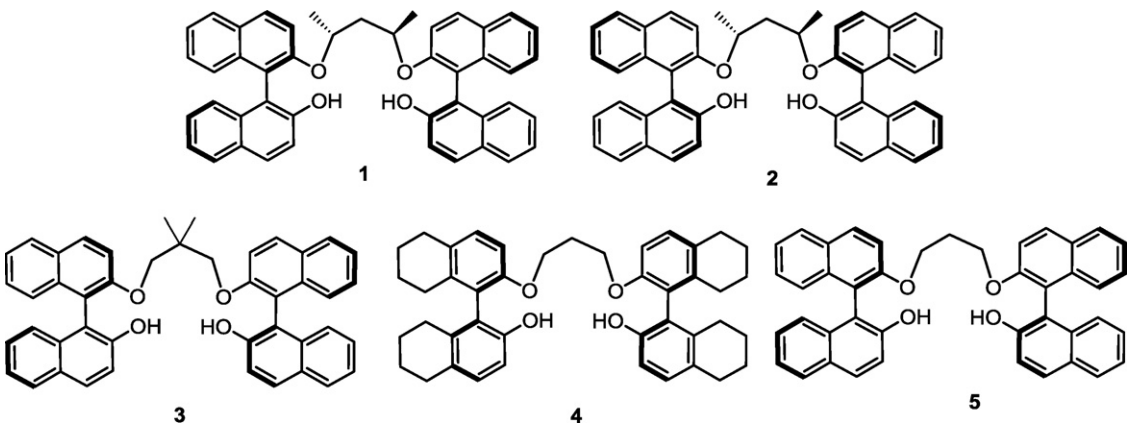
Results in Table 1 show that methyl substituents on the propyl ether bridge did not improve the performance of the ligands, since both the conversion and the *ee*, at 0 °C, are lower with ligands **1**–**3** (Table 1, entries 1–4), when compared with ligand **5** (Table 1, entry 5). Furthermore, these results also show that it is possible to predict the absolute configuration of the final alcohol depending essentially from the configuration of the BINOL moiety, with a moderated contribution of the stereogenic centers on the propyl ether bridge (53% ee of (*R*)-phenylpropanol and 30% ee of (*S*)-phenylpropanol, Table 1, entries 1 and 2, respectively).

Best conversions (97 and 99%) and enantioselectivities (81 and 62%) were achieved when the reaction was carried out with ligands **4** and **5** (Table 1, entries 4 and 5), which do not have any substituent in the propyl ether bridge. Furthermore, it should also be noticed that the enantioselectivity of the ethylation reaction is dependent from the temperature (−10, 0 and 40 °C), showing a maximum at 0 °C (Table 1, entries 5–7). These results are indicative that there are more than one catalytic active species in equilibrium, in solution.

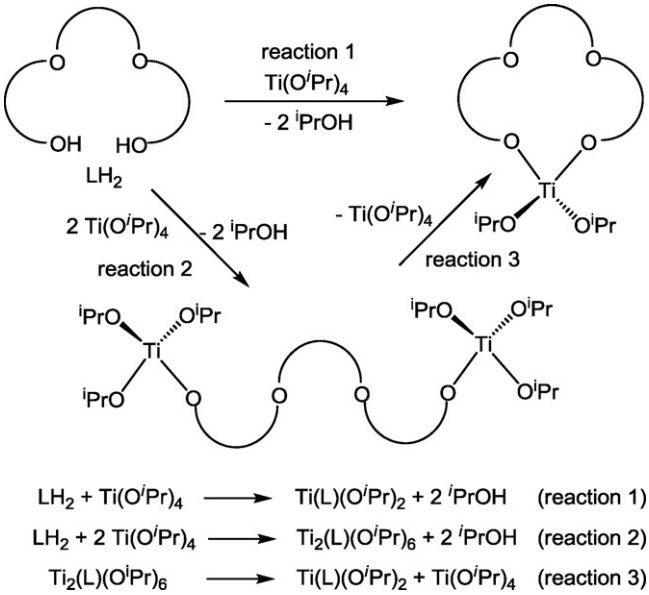
Since the titanium complexes of ligands **4** and **5** have showed the best results in the catalytic alkylation of benzaldehyde, the catalytic studies were extended to 2- and 3-chloro-benzaldehyde (**7** and **8** in Table 2, entries 5–12) using these ligands. In order to investigate the influence of the solvent polarity in the reaction performance, toluene (PhMe) and dichloromethane (DCM) were used as solvents. The results are collected in Table 2, and they show that in all cases the conversion is higher in reactions carried out in PhMe than those in DCM. However, contrary to the results previously described [5,6] there is only a small solvent effect on the enantioselectivity of the reactions, regardless of the ligand or the aldehyde used. Furthermore, a significant influence of the aldehyde structure on the *ee* was observed, being the *ee* of the alkylation of 2-chloro-benzaldehyde **7** significantly lower than those obtained with 3-chloro-benzaldehyde or benzaldehyde. From the overall results, it is possible to conclude that the best results are obtained with ligand 4 with aldehydes not substituted on the position 2 (Table 2, entries 1–4, 9–12).

3.3. Analysis of the chelation ability of the ligands via PM6 computational calculations

In order to correlate the relative preference of ligands towards the formation of a titanium chelate complex with their performance as co-catalyst, a theoretical computational study was carried out. The reaction enthalpies for the formation of two simplified model complexes, $Ti(L)(O^iPr)_2$ and $Ti_2(L)(O^iPr)_6$ (LH_2 = *bis*-BINOL-



Scheme 1.



Scheme 2.

2′,2″-ether ligands **1**–**5**), containing a chelating or a bridging ligand, respectively, were calculated and compared (Scheme 2). The conformational flexibility of these ligands made the choice of semiempirical quantum chemistry methods particularly adequate for this task. The recently developed PM6 hamiltonian [14], available in the MOPAC2009 software [15], which included parameterization for titanium, was chosen. This software has been successfully used in the simulation of a great variety of systems [16].

The main goal of this study was to evaluate the relative energy of each of the two alternative (open or chelate) complex products. An energetically favorable chelate for a given ligand is expected to show a greater enantioselectivity.

The first step of the study was to explore the conformational space of the ligands in order to identify the relevant most stable conformer or conformers with a significant population and determine their heats of formation. Then, the same procedure was carried out for both the bridging Ti$_2$(L)(O^{i}Pr)$_6$ and the chelate Ti(L)(O^{i}Pr)$_2$ species. The heats of formation of the conformers selected in the way described above were used in suitable isodesmic reactions that account for the energetic differences in the formation of the alternative complex products. Calculated reaction enthalpies for reactions 1–3 are collected in Table 3.

Table 3
Calculated reaction enthalpies for reactions 1–3 in Scheme 3.

Entry	Ligand	Reaction 1 (kJ mol^{-1})	Reaction 2 (kJ mol^{-1})	Reaction 3 (kJ mol^{-1})
1	**1**	15.0	−13.4	28.4
2	**2**	2.1	−5.1	7.2
3	**3**	−11.2	−18.7	7.5
4	**4**	−9.2	−3.0	−6.2
5	**5**	−11.2	−3.5	−7.7

These results indicate that the enthalpy for reaction 3 ($\Delta H_3 = \Delta H_1 - \Delta H_2$), that converts one mol of binuclear species in one mol of chelate complex plus one of Ti(O^{i}Pr)$_4$, is strongly dependent on nature of the ether bridge (Table 3). The enthalpic contribution favors the ligand chelated species Ti(L)(O^{i}Pr)$_2$ *versus* the bridged one only in the case of ligands **4** ($\Delta H_3 = -6.2$ kJ mol^{-1}) and **5** ($\Delta H_3 = -7.7$ kJ mol^{-1}) (Table 3, entries 4 and 5).

For the rest of ligands studied, enthalpy favors the formation of binuclear titanium with a bridging ligand.

Ligands **4** and **5** show exothermic processes for the formation of the chelated complex from Ti(O^{i}Pr)$_4$ and LH$_2$ ($\Delta H_1 = -9.5$ kJ mol^{-1} and $\Delta H_1 = -11.2$ kJ mol^{-1}, respectively), while for ligands **1** and **2** this process is endothermic, revealing steric restrictions in the formation of the chelate probably due to the presence of methyl groups in 1 and 3 positions of the propy ether bridge. Methyl groups at the position-2 in ligand **3** seem not to interfere with the formation of the chelate, since ΔH_1 for this ligand is nearly identical to that of ligand **5** (Table 3, entries 3 and 5). However, the formation of the chelate ligand **3**-titanium complex is not favored with respect to the ligand bridged species, since a very negative value of the ΔH_2 (-18.7 kJ mol^{-1}) was calculated. In summary, this theoretical calculations supports that the higher experimental enantioselectivity achieved with ligands **4** and **5**, correlates with the calculated higher chelation tendency of these two ligands.

Furthermore, the coordination of the ether fragments to the titanium was also tested, but its unfeasibility was observed due to steric constrains.

3.4. The nature of catalytic species

In order to gain some insight into the nature of the catalytic species, a number of techniques were tested, using the ligand **5**, as model. Firstly, the effect of the optical purity of the ligand on the stereoselectivity of the asymmetric alkylation of benzaldehyde was analyzed, using the simplified mathematical model developed by Kagan and co-workers [17] for catalytic species containing two chiral ligands, such as ML$_2$ or (ML)$_2$ complexes. In this case, a steady state involving three possible complexes, ML$_R$L$_R$, ML$_S$L$_S$, and ML$_R$L$_S$

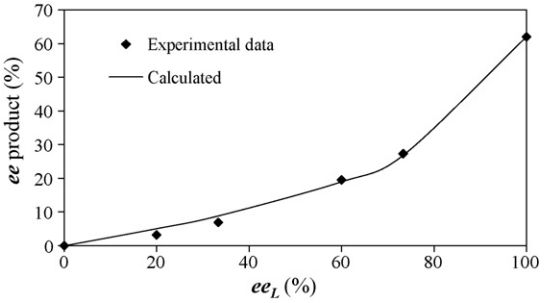


Fig. 1. Graphic representation of the *ee* of 1-phenylpropanol against *ee* of ligand 5.

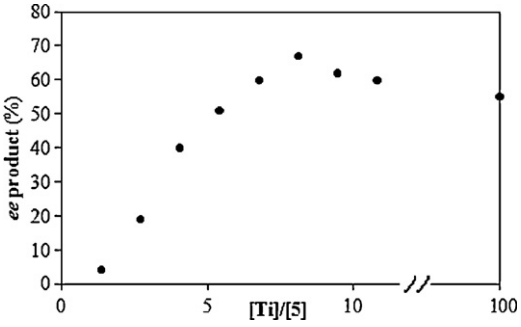


Fig. 2. Enantiomeric excess of (*R*)-1-phenylpropanol plotted against the $Ti(O^iPr)_4$/5 molar ratio on the catalytic alkylation of benzaldehyde in toluene. Reaction conditions are the same of Table 1. $T = 0\,^\circ C$.

is assumed, and the relation between the optical purity of the ligand ee_L, and that of the product of the reaction *ee* is shown in Eq. (1). In this equation, ee_o and *g* represent the enantiomeric excess achieved with the homochiral ligand, and the relative rate of the hetero- over the homochiral catalysts, respectively:

$$ee = \frac{2 \cdot ee_o \cdot ee_L}{1 + g + (1 - g) \cdot ee_L^2} \quad (1)$$

Fig. 1 shows the *ee* values of (*R*)-1-phenylpropanol obtained from enantiomerically enriched mixtures of ligand **5** plotted against the enantiomeric excess on the (*R*,*R*) isomer of this ligand (ee_L). The experimental values were fitted with a value of $g = 4$ in Eq. (1).

It is well established that a catalytic system with $g > 1$ points to a negative non-linear effect (−)-NLE, due to a greater reactivity of the *meso* (ML_RL_S) catalytic species *versus* the homochiral one [18]. Furthermore, this NLE indicates that the active catalytic species contains two ligands, in contrast with what was previously reported for the BINOL/$Ti(O^iPr)_4$ catalyst that contains two titanium ions bridged by a single BINOL ligand [9]. The activity of the background reaction (see last entry in Table 1) does not have any influence on the overall conclusion, since the amount of racemic phenylpropanol obtained is constant in all the experiments.

The effect of the Ti/L molar ratio on the *ee* of the product of the ethylation of benzaldehyde was also investigated and the results are represented in Fig. 2. These results show that at [**L**] = 25 mM, the *ee* of the product rises linearly with the Ti/L molar ratio, until *ca*. 8, for which the maximum stereoselectivity was reached. After this point, a smooth drop in the *ee* of the product was observed. This result reveals that a relatively large molar excess of $Ti(O^iPr)_4$, with regard to the ligand, is required to form a stereoselective catalyst. The requirement of an excess of titanium with 2′,2″-*bis*-BINOL-propyl ether ligand, to obtain higher *ee*, is in agreement with our recent results [11] and also the observations of others authors, using 3′3″-*bis*-BINOL [19] and also BINOL-type ligands [9].

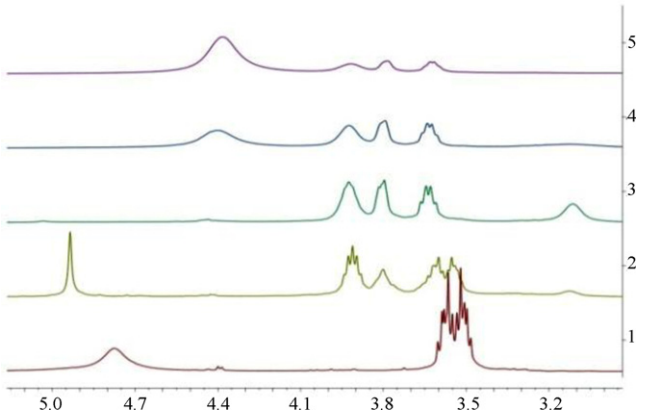


Fig. 3. ^1H NMR titration of 5 with $Ti(O^iPr)_4$. Solvent $CDCl_3$; $T = 25\,^\circ C$.

In an attempt to obtain complementary information about the nature of the catalytic active species, a ^1H NMR titration of the ligand with $Ti(O^iPr)_4$ was undertaken. Thus, to a $CDCl_3$ solution of ligand **5** (90 mM), successive amounts of $Ti(O^iPr)_4$ (0.5–4 equiv.) were added and the ^1H NMR spectra of the resulting solutions were recorded. Selected spectra of the aliphatic region ($\delta = 3.1$–5.1 ppm) are presented in Fig. 3. The ^1H NMR spectra of **5** shows a multiplet signal centered at 3.55 ppm assigned to the O–$CH_2CH_2CH_2$–O protons and a broad signal at 4.80 ppm assigned to the hydroxyl groups of the ligand, in addition to a multiplet at 1.53 from O–$CH_2CH_2CH_2$–O protons. After addition of 0.5 equivalents of $Ti(O^iPr)_4$, an evident decrease in the intensity of the signals at 3.55 and 4.80 ppm was observed, together with a downfield shift of both signals. At the same time, three new signals rose at 3.92, 3.80 and 3.65 ppm. The first corresponds to free isopropanol, while the other two are assigned to the diasteorotopic O–CH_2 protons of the ligand coordinated to the metal. The signal at 1.53 ppm is poorly sensitive to the coordination of the ligand. After further addition of 0.5 equivalents of $Ti(O^iPr)_4$ (Ti/L = 1), the signals from free ligand **5** disappeared, while a new broad signal rises at 3.15 ppm, which was attributed to the O$CH(CH_3)_2$ isopropoxide coordinated to the metal. The signals at 3.92, 3.80 and 3.65 ppm showed the same relative integration, and were assigned as two equivalents of O$CH(CH_3)_2$ from free isopropoxide, and two pairs of diastereotopic protons from the O–CH_2-ether bridge Ti–*bis*-BINOLate complex.

After addition of another equivalent of $Ti(O^iPr)_4$ (Ti/L = 2), a broadening of the overall spectra was observed, as well as a decrease in the 3.15 ppm signal, probably due to the fast exchange between the isopropoxide groups coordinated to the metal in the Ti–*bis*-BINOLate complex and those of $Ti(O^iPr)_4$. Further addition of $Ti(O^iPr)_4$ did not significantly change the spectra, except for the expected increase in the isopropoxide signal of $Ti(O^iPr)_4$ at 4.40 ppm. The most relevant result from the NMR study is the significant split of the signals of the diasteorotopic OCH_2 protons of the ligand that shows two clearly separated multiplets ($\Delta\delta$ *ca.* 0.15 ppm) when it is coordinated to the titanium. This is consistent with the formation of a complex with a chelated ligand that somewhat freezes the ligand conformation. Therefore, both ^1H NMR analysis and PM6 calculations point out that ligand **5** form a chelated titanium complex. Unfortunately, the fast isopropoxide ligands exchange in the NMR time scale did not allow the analysis of complexes formed at high Ti/ligand molar ratios.

To obtain conformational information, a titration of ligand **5** with $Ti(O^iPr)_4$ was carried out, but in this case circular dichroism spectra (CD) of the resulting solutions were analyzed. It is well established that CD of 1,1′-binaphthyl derivatives are extremely sensitive to the conformation that they adopt in solution, and in particular to the value of the dihedral angle θ between the

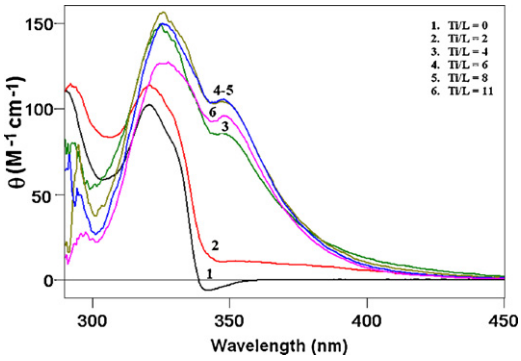


Fig. 4. CD spectra of the solutions of 5 and $Ti(O^iPr)_4$ at different molar ratios.

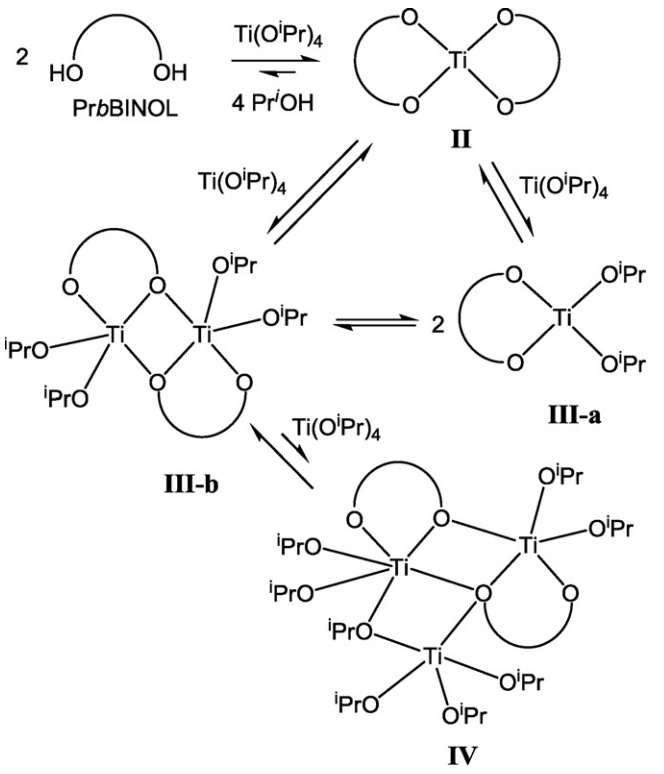
two naphthalene planes [6,10]. The evolution of CD spectra of a dichloromethane solution of ligand **5** (9.0×10^{-2} mM) titrated with $Ti(O^iPr)_4$ is shown in Fig. 4.

The CD spectrum of ligand **5** shows the characteristic intense positive couplet, due to the excitation coupling between long-axes polarized 1Bb transitions with a positive maximum at 325 nm (Fig. 4, spectrum 1). After addition of 2 equiv. of $Ti(O^iPr)_4$, almost no change in the shape and intensity of the band was observed (Fig. 4, spectrum 2). After the subsequent additions of $Ti(O^iPr)_4$ an increase in the intensity of the 325 nm band is observed, together with the appearance of a new positive band at 350 nm (Fig. 4, spectrum 3). The intensity of both bands steadily increases with the titanium concentration of the solutions until a Ti/ligand molar ratio *ca.* 6–8 (Fig. 4, spectra 4 and 5). At higher concentrations of $Ti(O^iPr)_4$, a broadening of the positive bands concomitantly with a decrease in the intensity is observed (Fig. 4, spectrum 6). These results points out to the existence of an equilibrium between species and one of them should be the predominant at the same Ti/ligand molar ratio (6–8) for which the best *ee* was achieved in the catalytic alkylation of benzaldehyde. Thus, this stereoselective catalytic species must be responsible for the band at 350 nm, as well as for the increase in the intensity of the band at 325 nm.

Further information about the nature of the species formed at different molar ratios of the ligand **5** and $Ti(O^iPr)_4$ was attained analyzing solutions of $Ti(O^iPr)_4$ and ligand **5** by ESI-MS. At the molar ratio $Ti(O^iPr)_4$/**5** = 0.5, one major species was observed, with a mass molecular cluster at 1267–1274 amu, and a 100% peak at 1269.2. This signal matches with the species $[TiL_2H]^+$ (II, Scheme 3), where L represents the deprotonated dianionic form of ligand **5**. At $Ti(O^iPr)_4$/**5** molar ratio equal to 1, besides the previous signal, two other clusters were observed. One at 710–720 amu with a 100% peak at 717.1, that matches with $[TiL(O^iPr)]^+$, which likely must arise from the species $[(TiL(O^iPr)_2)]$ (IIIa, Scheme 3). The other at 773.8–780.8 amu with a 100% peak at 777.8, is a definitive evidence for the formation of a species containing two ligands $[Ti_2L_2(O^iPr)_4H_2]^{2+}$, as required to explain the NLE described above (IIIb, Scheme 3)

This cluster corresponds to a doubly charged species, as evidenced by the 0.5 amu increments between isotopic peaks.

Since the species IIIb contains two chiral ligands, it could produce a NLE. However, from the catalytic results ploted in Fig. 2, the highest enantioselective species is only formed when the molar ratio is 8. Therefore, we propose that the catalytic species producing the highest *ee*'s is species IV (Scheme 3). This species can be formed by reaction of the binuclear species IIIb in the presence of an excess of $Ti(O^iPr)_4$. We assume that at low [Ti]/[**5**] molar ratio the equilibrium is shifted toward the bimetallic species IIIb. Finally, it should be pointed out that a large excess of $Ti(O^iPr)_4$ is required to obtain an high enantioselective species IV as the dominant one, like was previously observed for BINOL studies [5,6]. Further ESI-MS experiments at [Ti]/[**5**] molar ratios higher than 1 show evidence that polymerization occurs, preventing the full identification of species IV.



Scheme 3.

4. Conclusion

These studies allow us to conclude that titanium (IV)-*bis*-BINOLate-2′,2″-propylether complexes (**4** and **5**) yield the most stable Ti-chelates, leading to the best results in the ethylation of aryl aldehydes (*ca.* 80, 69%, respectively). The experimental results were corroborated by PM6 computacional calculations and ^1H NMR, which showed that ligands **4** and **5** have a higher chelating tendency.

A number of other techniques were used to investigate the nature of the catalytic species, formed in the reaction of ligand **5** with $Ti(O^iPr)_4$. The presence of two ligands in the catalytic active and selective species was corroborated by the observation of a negative NLE and by ESI-MS. Furthermore, experimental catalytic results as well as CD experiments showed that the most enantioselective species is formed only at Ti/ligand molar ratios close to 8. So, from the overall results a trinuclear complex $[Ti_3L_2(O^iPr)_8]$ (IV in Scheme 3) is proposed to be the most enantioselective catalytic active species.

The mechanistic overall results, especially the information obtained from computational calculations related to the chelating tendency of these type of ligands opens the way for further studies in order to design the ideal ligand structure to promote enantioselective catalytic reactions

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