Effect of water on BINOL/Ti(O^{i}Pr)$_4$ solution mixtures: The nature of a catalytic precursor of enantioselective sulfoxidation

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Abstract

The solution mixtures of (*R*)-BINOL, Ti(O^{i}Pr)$_4$ and H$_2$O in 1:0.5:10 proportion in CCl$_4$, corresponding to the conditions employed for catalyzing the enantioselective oxidation of sulfides to sulfoxides, contain a single titanium BINOLate species. NMR, CD and MS characterization allowed us to identify this species as (BINOLate)$_6$Ti$_4$(μ_3-OH)$_4$ with tetrahedric symmetry consistent with a known crystallographic structure. By varying sample preparation conditions, some aspects of the catalytic behavior could be rationalized. Using racemic BINOL, several heterochiral species were observed in accord with reported non-linear effects in catalysis.
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1. Introduction

Titanium (IV) complexes of 1,1′-bi-2(naphthol) (BINOL) represent one of the most powerful classes of enantioselective catalysts employed in modern organic synthesis [1]. An impressive variety of organic reactions promoted and stereocontrolled by BINOL/Ti species has been documented by recent reviews [1]; in fact, titanium dominates the literature of BINOL-based Lewis acids.

In addition to favorable electronic properties, the key factor responsible for the efficiency and versatility of BINOL/Ti catalysts is essentially structural, and arises from the combination of very special ligand and metal. On the one hand, the 1,1′-binaphthylic core is endowed with a typical structural pliancy, making it possible to accommodate donor atoms at 2,2′ positions into almost any required chelating (or bridging) geometry without substantial strain [2]. On the other hand, titanium alkoxides exhibit peculiar fluxionality in solution: they feature vari-

ous coordination numbers and geometries; undergo ligand addition, elimination and exchange reactions easily and rapidly; have a pronounced tendency to oligomerize and organize into composite supramolecular assemblies [3]. Such structural richness and complexity ensures flexibility and efficiency, but thwarts the efforts toward structural elucidations aimed at rationalizing catalytic behaviors. In particular, crystals amenable to X-ray analysis are not easily obtained, and the structural information relative to the solid state must be transferred with great caution to the solution state, where the majority of the reactions occur.

For example, BINOLates obtained by mixing BINOL and titanium (IV) halides, alkoxides and mixed halides/alkoxides, which embrace most of the synthetically useful BINOL/Ti complexes [1], may be represented by minimal formulae, such as "BINOLTiX$_2$" or "BINOLTi(OR)$_2$", which hardly have a correspondence with the true solution species [4,5]. First, depending on the ligand-to-metal ratio, a range of different stoichiometries is possible, e.g., "(BINOL)$_2$Ti", "(BINOL)TiX$_2$", "(BINOL)Ti$_2$X$_6$" and so on. Secondly, titanium expands its coordination number by addition of other available ligands or by forming oligomers upon sharing μ-donors. Finally, the initial complexes

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will possibly react with a variety of reagents, including adventitious ones: the most relevant example is water, which promotes formation of μ-oxo and μ-hydroxo compounds [3a]. As a result of the structural heterogeneity and of the role of many factors, hypotheses on the nature of active species and even catalytic precursors need to be substantiated by ad hoc investigations of solution samples as close as possible to the synthetic conditions [4,5]. In fact, BINOL/Ti catalysts are often prepared in situ by simple mixing of reagents and are not isolated [1], a situation which lends itself for direct spectroscopic measurements of the effective catalytically active solutions.

The identification of exact nature and structure of enantioselective catalysts or catalytic precursors is always a significant piece of information, because it may open the way to the rational design of new, more efficient chiral auxiliaries. In especially intriguing cases, the structural elucidation represents itself an important task from a spectroscopic point of view. In addition, chirality amplification phenomena [1,6,7] have often been observed in catalytic applications of titanium BINOLates (an aspect which is again related to structural features); thus, rationalization of non-linear effects (NLE) adds further theoretical interest to the study of this elusive family of compounds.

We have recently characterized, by means of NMR and circular dichroism (CD) spectroscopies, the samples obtained by dissolving enantiopure BINOL and excess titanium tetraisopropoxide $Ti(O^iPr)_4$ in anhydrous chloroform [4]. Such mixtures, when at least a 6:1 Ti-to-BINOL ratio is used, promote the enantioselective addition of dialkyl-Zn compounds to aldehydes [8]. Two different titanium BINOLates were detected to exist in the above conditions. At low (from 2:1 to 3:1) Ti/BINOL ratios, a dimeric 1:1 species dominates in solution, which can be formulated as [BINOLTi(O^{i}Pr)$_2$]$_2$; the solid-state compound obtained for the same stoichiometry is instead trimeric [5d]. At higher (from 3:1 on) Ti/BINOL ratios, the monomeric binuclear 2:1 species BINOLTi$_2$(O^{i}Pr)$_6$ is favored, and represents the active catalyst precursor [4,5d,5e,5f].

A system analogous to the above one has been found, first in 1992 by Uemura and coworkers, to catalyze the enantioselective oxidation of prochiral sulfides to sulfoxides by hydroperoxides in toluene or carbon tetrachloride [9]. Efficient catalysis requires a 2-fold excess BINOL with respect to $Ti(O^iPr)_4$, and the addition of a large (at least 10-fold with respect to BINOL) excess of water. Since chiral sulfoxides are useful synthons [10], the reaction has been widely applied in the following years and still attracts wide attention [11,12]; remarkable mechanistic aspects have also emerged [9b,9c,11c]. The reaction usually proceeds by two consecutive steps: the enantioselective sulfide oxidation to sulfoxides is followed by a kinetic resolution, which further enriches the product enantiomeric excess, by over-oxidizing the less favored sulfoxide enantiomer to the corresponding sulfone. Moreover, a distinct positive NLE has been reported with a peculiar relation between BINOL and sulfoxide enantiomeric excesses, which has drawn attention in

Kagan's and Blackmond's surveys on non-linear effects in catalysis [6].

Despite the undoubted interest, only a few direct indications are available on the nature of the titanium-containing active species. In the following we describe a spectroscopic characterization by NMR, CD and mass spectrometry of solution samples obtained in the same conditions as in the synthetic application. Our investigation led to several surprising results. First, despite the well-known complexity of BINOL/Ti(O^{i}Pr)$_4$ mixtures, especially at low Ti/BINOL ratios [4], a single stable species was detected. Second, this species proved to correspond to the μ-hydroxo tetranuclear complex (BINOLate)$_6$Ti$_4$(OH)$_4$, which had been previously isolated by Mikami et al. in the solid state and employed in [2+3] nitrone cycloadditions [13], but whose role in the enantioselective sulfoxidation had never been proposed before. In fact, Yudin and coworkers have solved the X-ray structure of the perfluorated analog "(F$_8$BINOLate)$_6$Ti$_4$O$_4$" [14] also employed as sulfoxidation catalyst [12a]; however, probably due the discrepancies observed in the catalytic behavior with respect to the parent BINOL catalyst, and to some structural differences, their conclusions had not been extrapolated to the general case.

2. Results

2.1. ^1H NMR spectra of 1:0.5:10 BINOL/Ti(O^{i}Pr)$_4$/H$_2$O in CCl$_4$

According to Uemura's procedure [9a,9b], the active catalyst for the enantioselective sulfoxidation is assembled by mixing BINOL, $Ti(O^iPr)_4$ and water in 1:0.5:10 proportion in toluene or CCl$_4$, with a BINOL concentration around 50 mM. Such catalyst is freshly prepared and stirred for one hour at room temperature before the reagents (sulfide and, thereafter, hydroperoxide) are added. Both the solvent and the amount of water are critical for the yield and selectivity; in particular, 5–20 equivalents of water relative to BINOL is the optimal amount [9a,9b]. Practically the same conditions have been employed in all successive applications of Uemura's procedure, using BINOL or its analogs [11,12]. Independent investigations have evidenced both a positive non-linear effect and the occurrence of a kinetic resolution of the sulfoxide [9b,9c,11c], following its formation (except for α-dialkylphosphonyl substrates) [11a,11e]. In the case of BINOL itself, no conclusive characterization of the catalytic mixture has been carried out; Naso and coworkers briefly reported to observe a dominant complex at NMR, whose resonances are affected by addition of water [11d]. The NMR spectra of similarly active mixtures of 5,5′,6,6′,7,7′,8,8′-octafluoroBINOL and Ti(O^{i}Pr)$_4$ have instead been reported by Yudin et al. [12a], and they will be referred to in Section 3.

The ^1H NMR spectrum of a 2:1 (R)-BINOL/Ti(O^{i}Pr)$_4$ mixture in CCl$_4$ (Fig. 1, bottom) displays dozens of small peaks plus the expected set of signals for free BINOL.
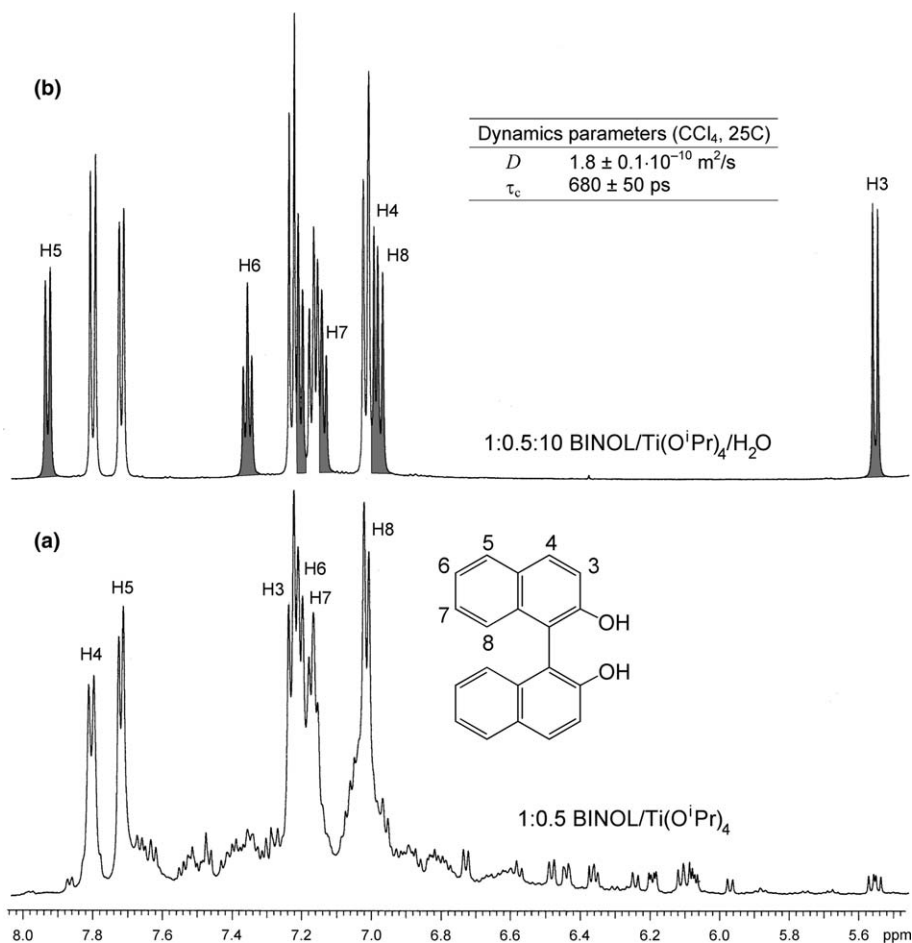
Fig. 1. ^1H NMR spectra (600 MHz) of (a) 1:0.5 (R)-BINOL/Ti(O^{i}Pr)$_4$ and (b) 1:0.5:10 (R)-BINOL/Ti(O^{i}Pr)$_4$/H$_2$O in CCl$_4$; BINOL concentration ≈50 mM. (a) Proton assignment showed for free BINOL; (b) proton assignment and parameters D and τ_c (inset, see text) showed for Ti-bound BINOL (filled peaks).

It is known that BINOL/Ti(O^{i}Pr)$_4$ mixtures with Ti-to-BINOL ratios up to 1–1.5 have complex NMR spectra descriptive of several species with distinct naphthalene rings [4]. However, addition of 5–20 equivalents of water with respect to BINOL provokes a dramatic spectral evolution (Fig. 1, top; shown for 10 H$_2$O equivalents added): a single set of new signals emerges, which may be assigned to a species containing two or more equivalent naphthalene rings. All aromatic protons undergo a significant shift upon complexation; especially notable is the high-field position of protons H3 and, to a minor extent, H4 (respectively, 1.6 and 0.8 ppm shift with respect to BINOL). At the same time, all the peaks relative to other BINOL/Ti species disappear: thus, addition of water promotes a complete convergence of a manifold of species into a single one; this is in accord with the experimental finding that water is necessary for the formation of the active catalyst, rather than for the following reactions [9b,9c]. It is widely established that water may convert titanium alkoxides and aryloxides into the corresponding oxo (or hydroxo) compounds with one or more oxygen atoms (or hydroxyl groups) bridging two or more distinct metal centers [3a]. The same behavior is also exhibited by titanium BINOLates: many active tita-

nium oxo/BINOLates have been described [15], and some isolated in the solid state [15e,16]. In particular, Mikami et al. reported the X-ray structure of the tetranuclear hydroxo complex (BINOLate)$_6$Ti$_4$(μ_3-OH)$_4$ (1) [13], obtained by hydrolysis either of the 1:1 complex "BINO-LTi(O^{i}Pr)$_2$" (actually trimeric) in refluxing THF, or of the tetranuclear dioxo complex (BINOLate)$_4$Ti$_4$(μ_3-O)$_2$(O^{i}Pr)$_4$ in hot toluene. By mixing (R)-BINOL, Ti(O^{i}Pr)$_4$ and H$_2$O in 1:0.5:10 proportion in CDCl$_3$ we recorded a ^1H NMR spectrum (not shown) coincident with the one reported by Mikami upon dissolution of solid 1 in d-chloroform [13]. This is the first indication that the sulfoxidation catalyst precursor is the same as compound 1, whose structure is showed in Fig. 2. The NMR equivalence of the twelve naphthyl rings is due to the high symmetry exhibited by 1, belonging to the T group; it is a static symmetry, not like a dynamic one, like that showed by other titanium BINOLates [4,5a,5e]. Cooling down the sample had no evident effect on its ^1H and HSQC spectra; moreover, no exchange between free and bound BINOLs could be detected by ROESY. The structure of 1 explains the high-field shift of H3 (and H4): each proton H3 lies exactly in front of another substituted benzene ring at less than
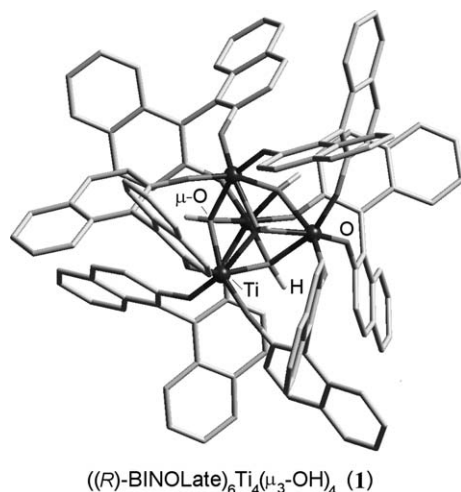
Fig. 2. Solid-state X-ray structure of $(BINOLate)_6Ti_4(\mu_3\text{-}OH)_4$ (**1**), adapted from [13]; aromatic hydrogens removed for clarity.

Fig. 3. ESI-MS spectrum of 1:0.5:10 (*R*)-BINOL/Ti(O^{i}Pr)$_4$/H$_2$O in CH$_3$CN; vertical bars show spectrum simulated for $[(BINOLate)_6Ti_4(OH)_4H]^+$, i.e., $(C_{120}H_{76}O_{16}Ti_4)H^+$.

3 Å, thus in a region subject to a strong shielding effect due to diamagnetic anisotropy. Similar ring current shift effects have been found for other titanium BINOLates with multiple 1,1′-bi-2(naphthol) moieties [4,15e].

2.2. DOSY, NOESY and ESI-MS data

The most characteristic property of **1**, i.e., its large molecular size, helped us to definitely assign its structure to the BINOL/Ti species found in our samples. First, the diffusion coefficient D measured by DOSY was extremely small (1.8 ± 0.1 and $3.1 \pm 0.1 \times 10^{-10}$ m^2/s in CCl$_4$ and CDCl$_3$, respectively, at 25 °C) [17]. When compared to the D values we measured for other titanium-BINOLates, [BINOLateTi(O^{i}Pr)$_2$]$_2$ and BINOLateTi$_2$(O^{i}Pr)$_6$ (respectively, 5.5 and 4.9×10^{-10} m^2/s in CDCl$_3$, 25 °C) [4], a clear-cut linear D vs. $1/V^{1/3}$ relationship emerges (see Supplementary material) when the molecular volume V estimated for **1** is used [18]. Other NMR parameters were also in keeping with slow molecular dynamics, in particular a very large rotational correlation time τ_c (about 700 ps in CCl$_4$, 25 °C) and NOESY cross-peaks having the same sign as diagonal ones (see Supplementary material). Finally, a mass ESI spectrum could be obtained by diluting in acetonitrile our 1:0.5:10 BINOL/Ti(O^{i}Pr)$_4$/H$_2$O solution in CCl$_4$; it showed a [M + H]$^+$ molecular cluster at 1962–1970 amu, with 100% peak at 1966.4, in keeping with what expected for $(BINOLate)_6Ti_4(OH)_4$ (Fig. 3). This is the ultimate proof that compound **1** is the only species, or by far the dominant BINOL/Ti species, obtained in the sulfoxidation conditions.

2.3. ^1H NMR spectra with different conditions

We varied the conditions of sample preparation to check the dependence of formation of **1** on the stoichiometry of reagents and on the solvent, with reference to the literature data. Concerning the sample ageing, the appearance of ^{1}H
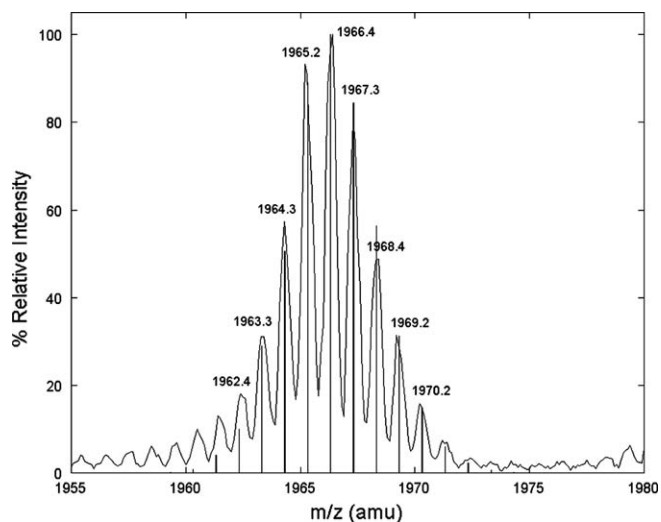
NMR peaks of **1** is immediate after addition of water to the BINOL/Ti(O^{i}Pr)$_4$ mixture; however, their relative intensity (with respect to free BINOL) increases with time: around a 50% enhancement of peaks of **1** is reached within a few hours, which justifies the need for stirring the catalytic mixture for one hour before substrate addition. Then, a plateau with almost 1:1 free/bound BINOL proportion is observed after about one week; afterwards, the sample is indefinitely stable (checked after 6 months storage at 0 °C). The optimal amount of water was confirmed to be 10 equivalents with respect to BINOL; 5 and 20 equivalents led to a slightly smaller relative amount of **1**. Since the BINOL-to-Ti stoichiometry in compound **1** is 6:4, we also prepared a BINOL/Ti(O^{i}Pr)$_4$/H$_2$O sample in 1:1:10 proportion, i.e., doubling the Ti(O^{i}Pr)$_4$ amount. Its ^{1}H NMR spectrum (see Supplementary material) is rich in dozens of peaks from 5.5 to 8.0 ppm which may be assigned to various BINOL/Ti species with D coefficients in the 1.4–2.5×10^{-10} m^2/s range (CCl$_4$, 25 °C) [19]; still, signals for **1** represent the most abundant set, with about 30% intensity relative to free BINOL. Concerning the solvents, we prepared samples in CCl$_4$, CDCl$_3$, d_8-THF, 9:1 d_{12}-cyclohexane/CDCl$_3$ and 1:1 CCl$_4$/CD$_3$CN [20]. Samples in chlorinated solvents and in their mixtures always displayed a single set of signals for bound BINOL, assigned to **1**. On the contrary, the sample in d_8-THF displayed four sets of naphthyl signals with equivalent intensity, relative to a single species with $D = 2.7 \pm 0.1 \times 10^{-10}$ m^2/s. Taking into account the different solvent viscosity [17], this species must be assigned to a structure different from **1**. Finally, racemic BINOL was used instead of enantiopure one to prepare 1:0.5:10 BINOL/Ti(O^{i}Pr)$_4$/H$_2$O samples in CCl$_4$, with the aim of assessing questions relative to non-linear effects (see Section 3). In these conditions, again, a very large number of peaks was obtained in the aromatic region (see Supplementary material), belonging to various

BINOL/Ti species with $D \approx 1.8 \pm 0.2 \times 10^{-10}$ m^2/s [19]. These include the homochiral compound equivalent to that obtained with enantiopure BINOL, containing six BINOLs of same configuration (which may be indicated as R_6 or S_6), and various heterochiral compounds (i.e., R_5S_1, R_4S_2 and so on). One must consider that the number of distinct non-equivalent naphthyl rings statistically expected for all possible heterochiral species amounts to 41 (see Supplementary material). Careful inspection of proton H3 resonance area (isolated from other protons), in DOSY and TOCSY spectra, revealed the presence of at least fifteen well-detected signals; remarkably, the one for the homochiral species is by far the most intense one. Moreover, its proportion sharply increases with time, while the signals for the other, heterochiral, species globally decrease; finally, the integral of homochiral species signals accounts for more than 50% of bound BINOL.

2.4. CD spectra

A CD spectrum of 1:0.5:10 (R)-BINOL/Ti(O^{i}Pr)$_4$/H$_2$O sample in 9:1 hexane/CDCl$_3$ is reported in Fig. 4, along with the spectrum of (R)-BINOL in the same solvent mixture. CD spectra of 1,1'-binaphthyl derivatives are extremely sensitive to the conformation they adopt in solution, and in particular to the value assumed by the dihedral angle θ between the two naphthalene planes [4,21], which may in principle vary between 50° and 130°. The CD spectra in Fig. 4 can be divided into two main regions. The 260–340 region features two positive CD bands for each spectrum, broadened by effect of vibronic states, assigned (from long to short wavelengths) to $\pi-\pi^*$ ^1L_b and ^1L_a electronic transitions of the 2-naphthoate chromophore [22]; the relative intensity increase and broaden-

ing upon titanium binding is mainly of electronic origin [4]. The 210–250 region features two very intense bands of opposite sign, defining a so-called negative couplet typical of (R)-1,1'-binaphthyl derivatives. It is mainly due to the exciton coupling between the ^1B_b electronic transitions of two attached 2-naphthoate rings, and its shape (sign, intensity and width) is strongly structure-dependent [21]. The couplet wavelength splitting $\Delta\lambda_{ext}$, i.e., the wavelength difference between the extremes of the two oppositely-signed components, is a relevant parameter strictly related to θ: ceteris paribus, the smaller is θ, the larger $\Delta\lambda_{ext}$ [4,21b,21c,21d,21e]. In the current case, the appearance of the two ^1B_b couplets in Fig. 4 is relatively similar. For the BINOL/Ti complex, the couplet looks strongly unsymmetrical, with a more intense negative branch, probably due a stronger coupling with other transitions; it is also partially blue shifted by about 3 nm with respect to free BINOL (seen at the crossover point, i.e. zero-CD point). More importantly, the apparent $\Delta\lambda_{ext}$ values are, respectively, 13.4 and 12.2 nm for bound and free BINOL ($\Delta\Delta\lambda_{ext} = 1.2$ nm); deconvoluting the CD couplet into the two theoretical components (by second derivative or multi-Gaussian fit), $\Delta\Delta\lambda_{ext} = 1.3$ nm is similarly found. This value is notably smaller than what encountered for other titanium BINOLates such as [BINOLateTi(O^{i}Pr)$_2$]$_2$ and BINOLateTi$_2$(O^{i}Pr)$_6$ ($\Delta\Delta\lambda_{ext} \approx 5$ nm) [4], in keeping with a different ligation mode. The bridging of a Ti–OH–Ti moiety by each pair of BINOL oxygens, as observed in 1 (Fig. 2), requires a wider 1,1'-binaphthyl dihedral angle θ than the chelation of a single Ti center; in fact, X-ray θ values amount to around 70° for 1 [23], and 55° for [BINOLateTi(O^{i}Pr)$_2$]$_2$ and BINOLateTi$_2$(O^{i}Pr)$_6$ [5d,5f]. Given the average orthogonal arrangement expected for BINOL ($\theta \approx 90°$) [22], the ^1B_b CD couplet for the present BINOL/Ti species is only slightly distorted with respect to the free ligand [24]. Thus, CD spectroscopy also supports a close structural relationship between the solid compound 1 and the BINOL/Ti solution species formed by mixing BINOL, Ti(O^{i}Pr)$_4$ and H$_2$O in 1:0.5:10 proportions.

3. Discussion

We have demonstrated the identity between the catalyst precursor obtained in the Uemura's sulfoxidation conditions [9] and compound 1 isolated and employed by Mikami in [2+3] nitrone cycloadditions [13]. At the best of our knowledge, this identity had been ignored so far and the nature of Uemura's enantioselective catalyst had remained unknown.

Yudin and coworkers solved the X-ray structures of two compounds obtained by mixing (R)-F$_8$BINOL and Ti(O^{i}Pr)$_4$ in 1:1 and 2:1 ratio [14]. The latter, reported as "C$_{120}$H$_{24}$F$_{48}$O$_{16}$Ti$_4$", has an X-ray structure similar to 1, if the four μ_3-oxo oxygens are replaced by μ_3-hydroxo groups (leading to an acceptable stoichiometry); it was obtained by heating, for one hour at 60 °C, a 2:1 (R)-F$_8$BINOL/Ti(O^{i}Pr)$_4$ solution in toluene and formally in
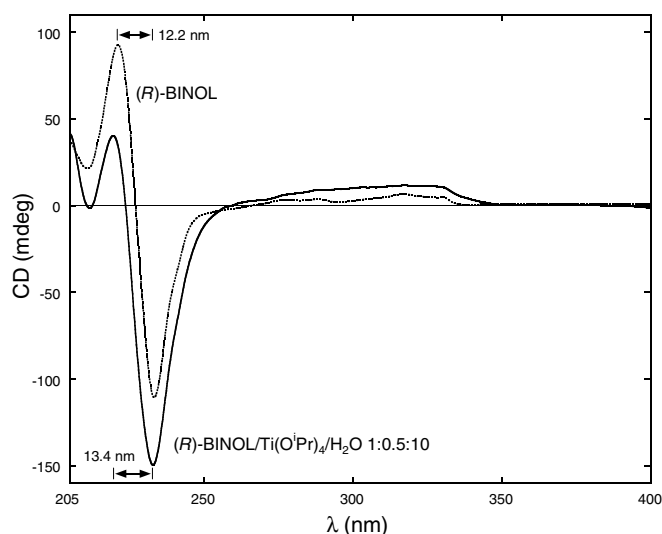

Fig. 4. CD spectra of (R)-BINOL and 1:0.5:10 (R)-BINOL/Ti(O^{i}Pr)$_4$/ H$_2$O in 9:1 hexane/CHCl$_3$. BINOL concentration ≈1 mM, cell 0.01 cm. Spectra are not normalized because of the uncertainty concerning the concentration of the BINOL/Ti species.

absence of water. In the enantioselective sulfoxidation of methyl-*p*-tolylsulfide with F_8BINOL as ligand, they used the same conditions as Uemura's [12a]. Probably because of the differences in the preparation, the correspondence between the two species in the solid and solution state is not explicit in the published papers [12a,14]. At the same time, the authors stressed the discrepancies between the titanium complexes of parent BINOL and its fluorinated analogs [12a,12b]. A most striking difference is that the opposite sense of induction in the enantioselective sulfoxidation was observed upon fluorine substitution: this phenomenon, which is not unique [12d,25], let them conclude that "upon coordination to Ti(IV), BINOL and F_8BINOL ligands produce very different catalytically active species" [14], and a "different aggregation is a likely cause for the change in the enantioselectivity" [12a]. In conclusion, there were various arguments pointing against a direct correspondence between BINOL- and F_8BINOL-based sulfoxidation catalysts. Our findings demonstrate, on the contrary, that if the titanium F_8BINOLate has a solution structure corresponding to the solid state, it must also closely resemble the titanium hydroxo-BINOLate in solution. Yudin et al. reported some NMR spectra for samples prepared without adding water, which do not compare well with ours; in fact, their 2:1 F_8BINOL/Ti(O^{i}Pr)$_4$ mixtures showed two sets of aromatic signals assigned to one C_2- and one C_1-symmetric species [12a,14].

Very recently, Kurosu et al. reported NMR and MS data for the 2:1 BINOL/Ti(O^{i}Pr)$_4$ mixture in dichloromethane in the presence of unactivated 4 Å molecular sieves [26], a set of conditions used to promote enantioselective aldehyde allylation, which is believed to produce titanium μ-oxo/BINOLate species similar to **1**. A molecular peak was detected at 1819 amu; the reported ^{1}H NMR spectrum displays many small signals for the aromatic protons, dispersed within a wide region (5.4–9.2 ppm) [26]. Thus, a high-nuclearity titanium cluster was obtained which seems not to coincide with **1**.

From a structural viewpoint, the nature of the solution species (BINOLate)$_6$Ti$_4$(μ$_3$-OH)$_4$ is amazing, with respect to its straightforward preparation. Simple mixing of the three reagents at room temperature leads to the composite architecture showed in Fig. 2; in particular, water is responsible for promoting a thorough re-organization of various BINOL/Ti species into a single one by forming four μ$_3$-hydroxo bridges. The presence of μ-oxo or μ-hydroxo groups is a common and well-recognized structural motif in the family of catalytically active titanium BINOLates [15]; in addition, it is possible that many described applications requiring the presence of molecular sieves [1] (particularly if not activated) actually involve μ-oxo/BINOLate species [15c,15d,15e,26]. In the current case, it is especially noteworthy how the mild conditions employed in the solution sample preparation lead to the same complex structure obtained upon crystallization of pre-heated mixtures [13]. Moreover, the compound (BINOLate)$_6$Ti$_4$(μ$_3$-OH)$_4$ has been demonstrated to form, in the

conditions required for the preparation of sulfoxidation catalyst, with strong preference with respect to any other BINOL/Ti species, and to be thermodynamically very stable and quite kinetically inert. During the course of sulfoxidation reaction, the generation of the true catalyst will presumably require that the precursor undergoes some ligand elimination/addition. This last point may partly explain why Uemura's catalyst is not the most active among those employed in sulfoxidations [10], while BINOL-based chiral auxiliaries perform as the most efficient ones in several described applications [1].

The NMR data obtained with racemic BINOL deserve further comment. They reveal the formation of a limited number of heterochiral species, and a strong preference for the homochiral complex. Many BINOL-derived chiral catalysts exhibit non-linear effects; interestingly enough, two recent authoritative reviews regarded the chirality amplification reported by Uemura as a remarkable case [6]. In fact, the enantioselective sulfoxidation/kinetic resolution sequence is itself a reason for the observed complicate relationship between sulfoxide and BINOL enantiomeric excesses. However, as noted by Blackmond, the scarce information on the catalytically active species has prevented any quantitative treatment of the case [6b]; the present identification of the catalyst precursor will hopefully remove this obstacle and prompt future analyses, although it is clear that considering the possible NLE's related to a species containing five or six BINOLates represents a formidable task.

4. Conclusion

The catalyst precursor obtained in the conditions designed by Uemura for enantioselective sulfoxidation, namely 1:0.5:10 BINOL/Ti(O^{i}Pr)$_4$/H$_2$O mixture in chlorinated solvents, is (BINOLate)$_6$Ti$_4$(OH)$_4$, and coincides with the solid compound **1**, previously isolated by Mikami in different conditions. NMR, MS and CD data concur to prove this substantial analogy between solution and solid-state structures. BINOL, titanium and water manifest a remarkable propensity to organize into an highly symmetrical and very stable solution compound, a point which may have an impact in the understanding of mechanistic aspects that regulate the assembling of titanium aryloxides in solution, with consequences on their catalytic behavior.

5. Experimental

All manipulations were carried out under an inert atmosphere. Racemic and (*R*)-1,1′-bi(2-naphthol) (e.e. >99%) were purchased from Fluka. Titanium (IV) isopropoxide (99.999% purity) was purchased from Aldrich. Solvents and reagents were purified with standard procedures.

NMR spectra were recorded with a Varian INOVA 600 spectrometer operating at 14.1 T. TOCSY (mixing time 80 ms), ROESY (800 ms) and HSQC spectra were acquired with standard pulse sequences. Rotational correlation times

τ_c were estimated using the known relation between cross-correlation rates, σ_{ij}, and τ_c for the pair of nuclei i and j at known distance [27], by means of 1D-NOESY experiments: protons H3 and H5 were selectively inverted with g3 pulses (duration 4 and 57 ms, B1 720 and 51 Hz, respectively); σ_{34}, σ_{54}, and σ_{56} were obtained by a linear fit of the NOE intensities vs. mixing time (0.1–0.5 s); the τ_c reported in the text and in Fig. 1 is the average of the values obtained from the three cross-relaxation rates. ^{1}H DOSY experiments were performed with the DgcsteSL pulse sequence, with gradient pulses having 2 ms width and 1.17–46.8 G cm^{-1} strength. For samples in CCl$_4$, an inner coaxial tube containing D$_2$O was used for the deuterium lock.

CD spectra were measured with a Jasco J715 spectropolarimeter, using a 0.01 cm cell, with the following conditions: speed 10 nm/min, response 2 s, band width 1.0 nm.

ESI-MS spectra were acquired with a PE Sciex API 4000 spectrometer, with the following conditions: scan range 1900–2700 amu, positive ion mode, ionspray voltage 5.0 kV, declustering potential 20 V, resolution 0.5 amu.

Acknowledgments

Appendix A. Supplementary material

Plot of experimental D coefficients vs. estimated $1/V^{1/3}$ for various BINOL/Ti species; ^{1}H NMR and HSQC spectra of 1:1:10 (R)-BINOL/Ti(O^{i}Pr)$_4$/H$_2$O and 1:0.5:10 rac-BINOL/Ti(O^{i}Pr)$_4$/H$_2$O in CCl$_4$; 1D-NOESY traces of 1:0.5:10 (R)-BINOL/Ti(O^{i}Pr)$_4$/H$_2$O in CCl$_4$; scheme of statistically expected homo/heterochiral analogs of **1** obtained with racemic BINOL (six pages). Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jorganchem.2005. 12.032.

References

[1] (a) J.M. Brunel, Chem. Rev. 105 (2005) 857–897;
(b) Y. Chen, S. Yekta, A.K. Yudin, Chem. Rev. 103 (2003) 3155–3211.

[2] (a) R. Noyori, H. Takaya, Chem. Scr. 25 (1985) 83–89;
(b) J.K. Whitesell, Chem. Rev. 89 (1989) 1581–1590.

[3] (a) D.C. Bradley, R.C. Mehrotra, I.P. Rothwell, A. Singh, Alkoxo and Aryloxo Derivatives of Metals, Academic Press, San Diego, 2001;
(b) Y.-T. Wu, Y.-C. Ho, C.-C. Lin, H.-M. Gau, Inorg. Chem. 35 (1996) 5948–5952.

[4] G. Pescitelli, L. Di Bari, P. Salvadori, Organometallics 23 (2004) 4223–4229.

[5] (a) T.J. Boyle, D.L. Barnes, J.A. Heppert, L. Morales, F. Takusagawa, Organometallics 11 (1992) 1112–1126;
(b) T.J. Boyle, N.W. Eilerts, J.A. Heppert, F. Takusagawa, Organometallics 13 (1994) 2218–2229;
(c) G.E. Keck, D. Krishnamurthy, J. Am. Chem. Soc. 117 (1995) 2363–2364;
(d) J. Balsells, T.J. Davis, P. Carroll, P.J. Walsh, J. Am. Chem. Soc. 124 (2002) 10336–10348;

(e) P.J. Walsh, Acc. Chem. Res. 36 (2003) 739–749;
(f) K.M. Waltz, P. Carroll, P.J. Walsh, Organometallics 23 (2004) 127–134.

[6] (a) See also the literature cited in [4], C. Girard, H.B. Kagan, Angew. Chem. Int. Ed. 37 (1998) 2922–2959;
(b) D.G. Blackmond, J. Am. Chem. Soc. 123 (2001) 545–553.

[7] Recent examples not included in the reviews [6]: (a) R. Villano, M. De Rosa, C. Salerno, A. Soriente, A. Scettri, Tetrahedron: Asymmetry 13 (2002) 1949–1952;
(b) H. Hanawa, T. Hashimoto, K. Maruoka, J. Am. Chem. Soc. 125 (2003) 1708–1709;
(c) H. Hanawa, D. Uraguchi, S. Konishi, T. Hashimoto, K. Maruoka, Chem. Eur. J. 9 (2003) 4405–4413;
(d) K. Mikami, Y. Matsumoto, Tetrahedron 60 (2004) 7715–7719;
(e) R. Villano, M.R. Acocella, M. De Rosa, A. Soriente, A. Scettri, Tetrahedron: Asymmetry 15 (2004) 2421–2424;
(f) M. De Rosa, M.R. Acocella, M.F. Rega, A. Scettri, Tetrahedron: Asymmetry 15 (2004) 3029–3033.

[8] (a) M. Mori, T. Nakai, Tetrahedron Lett. 38 (1997) 6233–6236;
(b) F.-Y. Zhang, C.-W. Yip, R. Cao, A.S.C. Chan, Tetrahedron: Asymmetry 8 (1997) 585–589.

[9] (a) N. Komatsu, Y. Nishibayashi, T. Sugita, S. Uemura, Tetrahedron Lett. 33 (1992) 5391–5394;
(b) N. Komatsu, M. Hashizume, T. Sugita, S. Uemura, J. Org. Chem. 58 (1993) 4529–4533;
(c) N. Komatsu, M. Hashizume, T. Sugita, S. Uemura, J. Org. Chem. 58 (1993) 7624–7626.

[10] H.B. Kagan, in: I. Ojima (Ed.), Catalytic Asymmetric Synthesis, second ed., Wiley, New York, 2000, pp. 327–356 (Chapter 6C).

[11] (a) M.A.M. Capozzi, C. Cardellicchio, G. Fracchiolla, F. Naso, P. Tortorella, J. Am. Chem. Soc. 121 (1999) 4708–4709;
(b) A. Massa, A. Lattanzi, F.R. Siniscalchi, A. Scettri, Tetrahedron: Asymmetry 12 (2001) 2775–2777;
(c) A. Massa, F.R. Siniscalchi, V. Bugatti, A. Lattanzi, A. Scettri, Tetrahedron: Asymmetry 13 (2002) 1277–1283;
(d) M.A.M. Capozzi, C. Cardellicchio, F. Naso, V. Rosito, J. Org. Chem. 67 (2002) 7289–7294;
(e) C. Cardellicchio, F. Naso, M.A.M. Capozzi, Tetrahedron: Asymmetry 15 (2004) 1471–1476;
(f) X. Jia, X. Li, L. Xu, Y. Li, Q. Shi, T.-L. Au-Yeung, C.W. Yip, X. Yao, A.S.C. Chan, Adv. Synth. Catal. 346 (2004) 723–726.

[12] With partially fluorinated BINOLs: (a) L.J.P. Martyn, S. Pandiaraju, A.K. Yudin, J. Organomet. Chem. 603 (2000) 98–104;
(b) S. Yekta, L.B. Krasnova, B. Mariampillai, C.J. Picard, G. Chen, S. Pandiaraju, A.K. Yudin, J. Fluorine Chem. 125 (2004) 517–525;
(c) Y. Chen, S. Yekta, L.J.P. Martyn, J. Zheng, A.K. Yudin, Org. Lett. 2 (2000) 3433–3436;
With other modified BINOLs: (d) M.T. Reetz, C. Merk, G. Naberfeld, J. Rudolph, N. Griebenow, R. Goddard, Tetrahedron Lett. 38 (1997) 5273–5276;
(e) C. Bolm, O.A.G. Dabard, Synlett 3 (1999) 360–362;
With solid-supported BINOL derivatives: (f) B.H. Lipshutz, Y.-J. Shin, Tetrahedron Lett. 41 (2000) 9515–9521;
(g) X. Wang, X. Wang, H. Guo, Z. Wang, K. Ding, Chem. Eur. J. 11 (2005) 4078–4088.

[13] K. Mikami, M. Ueki, Y. Matsumoto, M. Terada, Chirality 13 (2001) 541–544.

[14] S. Pandiaraju, A. Lough, A.K. Yudin, Israel J. Chem. 41 (2001) 309–312.

[15] (a) M. Terada, K. Mikami, J. Chem. Soc., Chem. Commun. (1994) 833–834;
(b) D. Kitamoto, H. Imma, T. Nakai, Tetrahedron Lett. 36 (1995) 1861–1864;
(c) M. Terada, Y. Matsumoto, Y. Nakamura, K. Mikami, Chem. Commun. (1997) 281–282;
(d) K. Mikami, M. Terada, Y. Matsumoto, M. Tanaka, Y. Nakamura, Micropor. Mesopor. Mater. 21 (1998) 461–466;

(e) M. Terada, Y. Matsumoto, Y. Nakamura, K. Mikami, Inorg. Chim. Acta 296 (1999) 267–272;

(f) H. Hanawa, T. Hashimoto, K. Maruoka, J. Am. Chem. Soc. 125 (2003) 1708–1709;

(g) Ref. [7c];

(h) T. Kano, T. Hashimoto, K. Maruoka, J. Am. Chem. Soc. 127 (2005) 11926–11927.

[16] T.C.H. Lam, E.Y.Y. Chan, W.-L. Mak, S.M.F. Lo, I.D. Williams, W.-T. Wong, W.-H. Leung, Inorg. Chem. 42 (2003) 1842–1847.

[17] Solvent viscosities in cP (1 cP = 10^{-3} Pa s) at 25 °C: CCl$_4$, 0.90; CHCl$_3$, 0.53; THF, 0.46. Available from <http://www.meta-chem.com/tech/hplc-solvent.html>.

[18] Molecular volumes were estimated with Spartan'04, Wavefunction Inc., Irvine, CA.

[19] Processing of DOSY spectra with overlapping peaks leads to poorly accurate D values, therefore the reported quantities are only indicative.

[20] The two solvent mixtures were taken into account to check the consistency between the species detected in CCl$_4$ or CDCl$_3$ with those present in the samples used for CD and MS.

[21] (a) S.F. Mason, R.H. Seal, D.R. Roberts, Tetrahedron 30 (1974) 1671–1682;

(b) L. Di Bari, G. Pescitelli, P. Salvadori, J. Am. Chem. Soc. 121 (1999) 7998–8004;

(c) L. Di Bari, G. Pescitelli, F. Marchetti, P. Salvadori, J. Am. Chem. Soc. 122 (2000) 6395–6398;

(d) L. Di Bari, G. Pescitelli, G. Reginato, P. Salvadori, Chirality 13 (2001) 548–555;

(e) L. Di Bari, M. Lelli, G. Pintacuda, G. Pescitelli, F. Marchetti, P. Salvadori, J. Am. Chem. Soc. 125 (2003) 5549–5558.

[22] I. Hanazaki, H. Akimoto, J. Am. Chem. Soc. 94 (1972) 4102–4106.

[23] Exactly, 65–67° (if 2-1-1′-2′ dihedrals are considered) or 70–74° (9-1-1′-9′ dihedrals) [13].

[24] The CD spectrum of BINOL/Ti species is dominated by the exciton coupling between directly attached naphthol rings (6 intra-binaphthylic terms); however, due to the proximity between non-directly attached naphthols in 1, some of the relative couplings (54 inter-binaphthylic terms) are also very strong. Calculations of CD spectra on the X-ray structure of (R)-1 with the DeVoe method predict an overall positive couplet due to inter-binaphthylic couplings, which combines with the negative one predicted for the intra-binaphthylic couplings, resulting into an overall negative couplet with both reduced intensity and wavelength splitting (3 nm smaller) with respect to that due to intra-binaphthylic terms alone. For references on DeVoe-type calculations, see [21b,21c,21d,21e] and: S. Superchi, E. Giorgio, C. Rosini, Chirality 16 (2004) 422–451.

[25] S. Superchi, M.I. Donnoli, C. Rosini, Tetrahedron Lett. 39 (46) (1998) 8541–8544.

[26] M. Kurosu, M. Lorca, Synlett 7 (2005) 1109–1112.

[27] M.H. Levitt, Spin Dynamics, Wiley, Chichester, 2001 (Chapter 16.4).