Structure Investigation of Ti^{IV}-BODOLates Involved in the Catalytic Asymmetric Reduction of Ketones Using Catecholborane

Ian Sarvary,[a] Per-Ola Norrby,*[b] and Torbjörn Frejd*[a]

Abstract: The complexes formed by the reaction of $[Ti(OiPr)_4]$ and bicyclo-octanediols (BODOLs) **1** and **2** (1:1) are useful as chiral catalysts in asymmetric reductions and were investigated by ^1H NMR spectroscopy and computational methods. A consistent picture emerged of head-to-tail dimers being kept together via a Ti-O-Ti-O μ-oxo bridge similar to the Ti-tartrates but different from the corresponding Ti-BINOLates and Ti-TADDOLates.

Keywords: asymmetric catalysis · computer chemistry · diol ligands · reduction · titanium

Introduction

The versatility of titanium diolates as catalysts in asymmetric synthesis has motivated considerable interest in their structural and dynamic behavior; one of the most studied group of Ti^{IV} complexes is the alkoxides.[1] Of particular interest was the discovery by Sharpless and Katsuki in 1980 that Ti-tartrates worked amazingly well as catalysts in asymmetric epoxidation of allylic alcohols.[2] Other Ti-diolates based on BINOLs and TADDOLs have been established as benchmark catalysts for various other enantioselective reactions.[3]

As suggested by Sharpless and Finn the major titanium–tartrate in solution formed by mixing diethyltartrate with $[Ti(OiPr)_4]$ in a 1:1 ratio is a μ-oxo bridged dimer of the M_2L_2-type (Figure 1a).[4] Very recently the crystal structure of a 1:1 complex between BINOL and $[Ti(OiPr)_4]$ formed in chloroform was reported with high resolution and shown to be a trimer of composition $[(BINOLate)Ti(OiPr)_2]_3 \cdot CHCl_3$ (Figure 1b).[5] The four-membered μ-oxo bridging motif was present in both the tartrate and the BINOL complexes. On the other hand this motif was apparently not present in the corresponding Ti-TADDOLate. In this case the structure was shown to be a monomeric Ti-diolate of composition

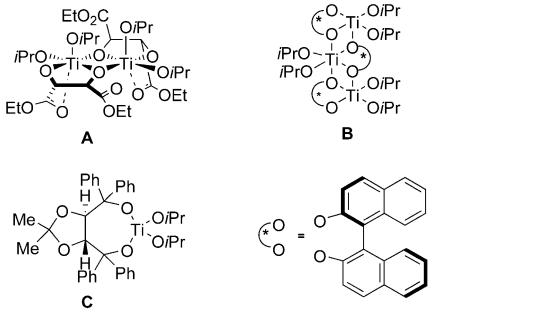

Figure 1. Schematic representations of the a) Ti-tartrate, b) Ti-BINOLate and c) Ti-TADDOLate formed with a 1:1 stoichiometry of diol and $[Ti(OiPr)_4]$.

$[(TADDOLate)Ti(OiPr)_2]$ (Figure 1c).[6] It should be noted that the structure and composition of the complexes formed are strongly dependent on the diol to $[Ti(OiPr)_4]$ ratio used on mixing the components. In this report we will focus on the 1:1 complexes, which do not contain halogens or semi-hydrated alcoholates. Such complexes are also of considerable interest as catalysts and have been investigated.[7]

In the examples shown above, and in most other cases of titanium–alcoholates used in catalysis, 1,2- or 1,4-diols have been used a chiral ligands, while only few examples are found for 1,3-diols. As the overall composition and structure of titanium diolates are very dependent on the structure of the diol we were interested in studying the behavior of Ti-diolates based on some bicyclic 1,3-diols that were available to us. Some time ago we found that a catalytic system based on *b*icyclic[2.2.2]*o*ctane*diol*s (BODOL) **1** or **2** (Figure 2) together with $[Ti(OiPr)_4]$ worked well in asymmetric catalytic reductions of ketones using catecholborane as the reducing agent.[8,9] Wandrey et al. have already applied diol ligands of the TADDOL-type earlier, and used these under general re-

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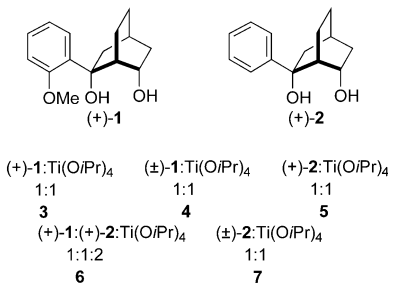

Figure 2. BODOL ligands and complex compositions investigated.

action conditions.[10] We found that the BODOLs gave higher *ee* values than the TADDOLs and became curious about the details of this reaction.

Apparently, very different structures may result from the mixing of a diol and $[Ti(OiPr)_4]$, even at a 1:1 ratio, depending on the structure of the diol and the method of preparation. This observation encouraged an investigation of Ti-BODOLates, which may be regarded as precatalysts in the catalytic asymmetric reduction of ketones with catecholborane. Coordination of BODOL **1** to Ti^{IV} would result in noticeable ^1H NMR chemical shifts of several of its resonances. This was indeed the case and was already mentioned in our earlier report.[9] In continuation of this work we now present evidence for a M_2L_2 complex being formed in situ under the conditions of the reduction. Since it was not possible to obtain crystalline complexes suitable for X-ray diffraction, this investigation is based upon NMR spectroscopy together with computational chemistry. The lack of crystal structures is not a disadvantage as structural information of complexes in solution may have a better bearing on the actual catalyst, which still may be impossible to identify with a high degree of accuracy.

The following convention is being used throughout this report: the complex formed from (+)-**1** and $[Ti(OiPr)_4]$ 1:1 is complex **3**, the corresponding diastereomeric complex formed from (±)-**1** is **4**, that from (+)-**2** is **5**, the mixed complex formed from (+)-**1**, (+)-**2** and $[Ti(OiPr)_4]$ is complex **6** and the complex of (±)-**2** is **7**.

Results and Discussion

To investigate the stoichiometry of the complex formed between **1** and $[Ti(OiPr)_4]$ ^1H NMR spectra were recorded in $[D_6]$benzene solutions of **1**, to which increasing amounts of $[Ti(OiPr)_4]$ were added in portions of 0.1 equivalents (Figure 3). Already after the first portion, the OH signals at δ 4.40 and 4.50 ppm were broadened, but no other changes of the spectrum of the free ligand were observed (Figure 3, trace B). Peaks from displaced *i*PrOH were present as indicated by the signal at δ3.80 ppm. This spectral appearance

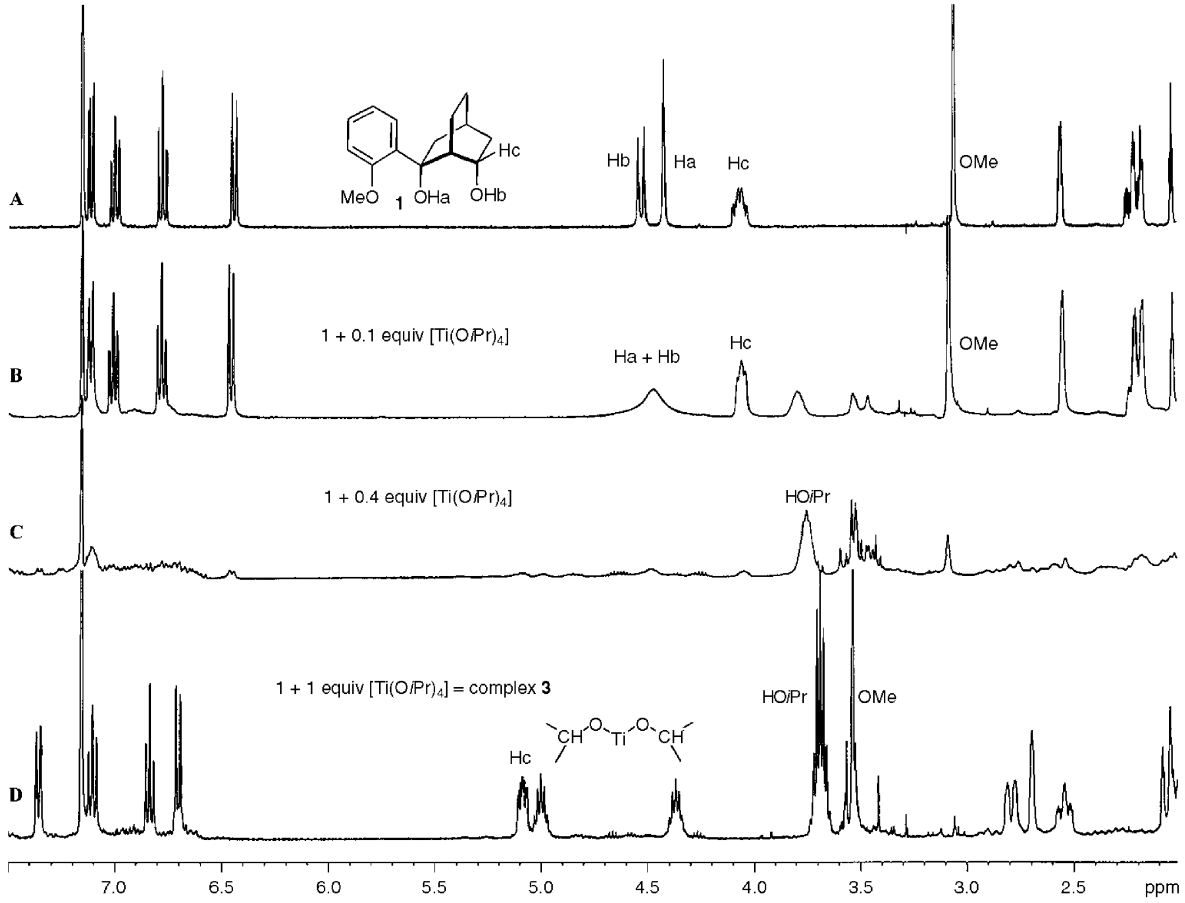

Figure 3. A) Free ligand **1**, B) **1** with 0.1 equiv $[Ti(OiPr)_4]$, C) **1** with 0.4 equiv $[Ti(OiPr)_4]$, and D) **1** with 1 equiv $[Ti(OiPr)_4]$ (complex **3**).

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remained essentially the same until 0.4 equivalents of [Ti(O*i*Pr)$_4$] were added, except that the peak amplitude of the resonances of **1** gradually decreased, and the signals from the displaced *i*PrOH increased (Figure 3, trace C). The reduction in the amplitude of **1** is clearly seen in the aromatic region where several broad peaks of low amplitude appeared.

At the 0.5 equivalent level the spectrum of the ligand had almost disappeared (not shown). This may be due to a slow exchange; however, an increase of the temperature to +85 °C, or decrease to −65 °C did not result in noticeable changes in the spectrum. (The temperature dependent NMR spectra were recorded in [D$_8$]toluene as this allowed a broader temperature range in the NMR experiments. The NMR spectra from the titration were identical for toluene and benzene, although the spectral quality was better in benzene.) A more plausible explanation is the formation of oligomeric or polymeric compounds, which may not give a clear NMR spectrum under normal NMR conditions. Thus, larger aggregates may be formed at the 2:1 ratio of **1** to [Ti(O*i*Pr)$_4$] and therefore it is not likely that that a well defined complex of the TiL$_2$-type exists.

A new set of sharp lines, substantially shifted towards lower field, gradually appeared upon increasing amounts of [Ti(O*i*Pr)$_4$] beyond the 0.5 equivalent level. At 1 equivalent a clear spectrum appeared, which seemed to originate from a single complex. It should be noted that two different CH heptets of Ti-coordinated isopropoxides were clearly seen at δ 4.4 and 5.0 ppm, respectively (Figure 3, trace D). The NMR spectrum of the 1:1 complex did not change upon increasing the temperature from −65 to +85 °C or the reverse; this shows that the complex is rather stable during the relatively short period of time required for NMR recording and that we are far from coalescence.

Further addition of [Ti(O*i*Pr)$_4$], up to 3 equivalents, or the addition of more *i*PrOH (4 equiv) did not result in any significant changes in the spectrum. Thus, a complex with the general composition [BODOLate/Ti(O*i*Pr)$_2$] seemed to be indicated, although the number of such units could not be determined at this point. The insensitivity of the spectral appearance on addition of additional amounts of [Ti(O*i*Pr)$_4$] was surprising since other complexes would be expected in light of what has been reported in the literature. For example, a reagent made from a 2:1 Ti/tartrate mixture was used for the chlorohydroxylation of allylic alcohols that shows the opposite enantiofacial selectivity compared with the 1:1 complex.[11] Moreover, the BINOL and the TADDOL systems gave quite different complexes depending on the Ti:diol ratios.[5,6]

The fact that resonances of only one type of BODOL unit was observed implied that the complex had a high symmetry. The two non-equivalent isopropyl group signals indicated that we were examining a single complex, and not an average signal from multiple complexes. A rapid complex equilibration would most likely also render the isopropyl groups equivalent, and a monomeric complex would be expected to show rapid associative exchange of the isopropoxy groups. As this is not observed, the most likely composition seems to be a dimer with C_2 symmetry.

Unfortunately, no information regarding the composition of the complex could be obtained by mass spectroscopy (EI, FAB and ESP). Only a variety of mass peaks were observed over a large interval, none of which could be regarded as relevant. We therefore used NMR spectroscopy to try to establish the composition of the complex. As mentioned above, the Ti-coordinated diol **1** showed several downfield shifts in comparison with the free ligand.

The largest change was observed for the H$_c$ resonance, which shifted from δ 4.05 to 5.10 ppm. Also, a large downfield shift for the signal of OMe was noted, from δ 3.05 to 3.55 ppm. Minor downfield shifts were noticed for the aromatic signals (0.1–0.3 ppm), as well as for the bicyclic signals.

We previously reported a positive nonlinear effect (NLE) for the reduction of acetophenone with catecholborane catalyzed by 10 mol % of a complex presumably formed from a 1:1 mixture of **1** and [Ti(O*i*Pr)$_4$].[9] The NLE indicated that at least two ligands were involved in the catalytic system, which may be denoted ML$_n$. (We have used the original (M) notation from Kagan, in which M denotes the metal part of the catalyst and includes achiral ligands such as *i*PrO.) The presence of two or more ligands in the catalyst offered the possibility to assemble diastereomeric complexes if the ligand is supplied as a mixture of enantiomers. As a consequence, one would expect a difference in catalytic activity of the homochiral versus the heterochiral complexes as well as different sets of lines in their NMR spectra. The NLE model of Kagan et al.[12] involves ML$_n$ complexes as catalysts, which is in line with our observations. This model is often suggested when NLEs are present in Ti^{IV}-catalyzed reactions. An extension of Kagans ML$_n$ model was introduced by Noyori et al.[13] and is often cited in cases where NLEs have been noted in the R$_2$Zn addition to aldehydes catalyzed by amino alcohols. In this model the dimers (or larger aggregates) are supposed to be catalytically inactive, but are in equilibria with the monomeric enantiomers of the respective catalytically active species. The basis for a NLE then lies in the different equilibria between the diastereomeric dimers and the enantiomeric monomers. Thus, even though we have determined a positive NLE this does not prove that the true catalyst was of the (M)L$_n$ type since it could also be an ML catalyst according to the Noyori model.

As mentioned, an (M)L$_n$ complex using scalemic mixtures of **1** together with an equimolar amount of [Ti(O*i*Pr)$_4$] would give NMR signals for at least two diastereomeric complexes. Indeed, two such sets of signals were observed as we previously reported.[9] One set was from the previously observed complex while the new set of signals was different but similar, suggesting the formation of a diastereomeric complex. A new peak at δ 7.3 ppm and other peaks shadowing the aromatic peaks, as well as a new methoxy signal at δ 3.6 ppm revealed this new complex. Also, a new set of peaks was present in the region of $\delta = 2.9$–2.4.

At this stage a (TiL)$_2$/2TiL equilibrium model for the composition of the complex seemed justified as a first approximation based on: 1) the 1:1 stoichiometry of the complex as revealed by the NMR titration and that no free ligand could be observed, 2) the formation of two diaster-

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eomers using scalemic **1**, 3) the possibility of a C_2-symmetric complex and 4) the NLE. This equilibrium model is compatible with the NMR data and the following alternatives could be considered:

a) Homochiral and heterochiral complexes originating from the composition M_2L_2:

$$(+)\text{-}\mathbf{1} + (\pm)\text{-}\mathbf{1} + \mathrm{Ti} \rightleftharpoons (+)\text{-}\mathbf{1}_2\,\mathrm{Ti}_2 + (+)\text{-}\mathbf{1}\,\mathrm{Ti}_2\,(-)\text{-}\mathbf{1} + (-)\mathbf{1}_2\,\mathrm{Ti}_2$$

b) A monomeric (enantiomeric) complex together with a dimeric heterochiral complex.

$$(+)\text{-}\mathbf{1} + (\pm)\text{-}\mathbf{1} + \mathrm{Ti} \rightleftharpoons (+)\text{-}\mathbf{1}\,\mathrm{Ti} + (+)\text{-}\mathbf{1}\,\mathrm{Ti}_2\,(-)\text{-}\mathbf{1}$$

To distinguish between alternatives a) and b), a mixed complex from a solution of (+)-**1** and (+)-**2** together with [Ti(O*i*Pr)$_4$] was prepared (in the ratios 1:1:2). This resulted in the formation of three different, but similar spectra (Figure 4). Two of these spectra were identical to those of the separate Ti-complexes **3** and **5**. This is shown in Figure 4 traces A and B, respectively. The new spectrum originated from a third complex, and shares the spectral features of previous spectra (Figure 4 trace C). The only peak which was not affected appeared at δ 6.70 ppm (originating from **3**). Thus, we believe that the new set of signals originated from a complex **6** with a ratio of (+)-**1**:(+)-**2**:Ti$_2$. As a consequence, it seems likely that all of our complexes were of the dimeric Ti_2L_2-type.

The complexes in Figure 4 trace C (**3**, **5** and **6**), were formed with the integral ratio 1:1:1, which fits the statistical formation of these complexes very well, assuming an equilibrium constant close to 1. (Due to the C_1 symmetry of the mixed complex, the relative integrals of the signals of this complex were $^1/_2$ of the intensity noted for the complexes of only **1** and **2**.) Ti-alcoholates are known to rapidly exchange ligands and in our case a fast exchange between the complexes was also indicated by the following experiment. Two separate solutions of **3** and **5** were mixed, resulting in an identical spectrum (Figure 4C). As the 1:1:1 mixture of the three complexes was formed within minutes a rapid exchange of ligands was evident. The equilibrium system of the components is shown below. As no NMR signals could be detected for the free ligands when combined with an equimolar portion of [Ti(O*i*Pr)$_4$] the equilibrium constants for the formation of the complexes (K_1–K_3) should be much greater than unity. Moreover, the formation of the mixed complex, together with the ligand-homogeneous complexes in the 1:1:1 ratio, as depicted in the last equation, strongly indicates that the equilibrium constant K_4 was ≈ 1.

The equilibria of the Ti complexes investigated between the ligands **1** and **2** and Ti(O*i*Pr)$_4$ are given in the following equations:

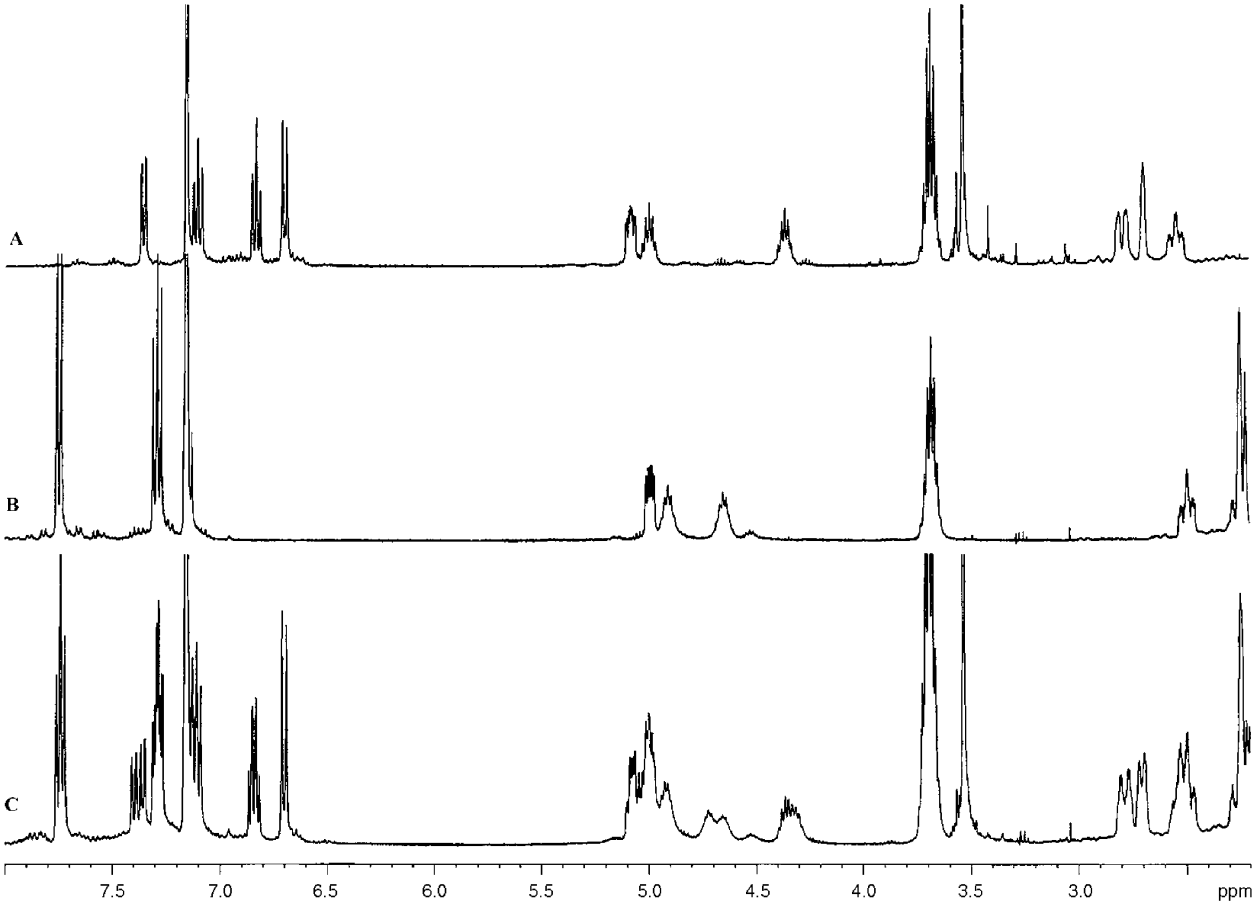

Figure 4. The complex **3** (A), complex **5** (B), the mixture of complexes **3**, **5** and **6** (C).

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$$2\,(+)\text{-}\mathbf{1} + 2\mathrm{Ti} \rightleftharpoons (+)\text{-}\mathbf{1}_2\,\mathrm{Ti}_2 \qquad K_1 \gg 1$$

$$2\,(+)\text{-}\mathbf{2} + 2\mathrm{Ti} \rightleftharpoons (+)\text{-}\mathbf{2}_2\,\mathrm{Ti}_2 \qquad K_2 \gg 1$$

$$(+)\text{-}\mathbf{1} + (+)\text{-}\mathbf{2} + 2\mathrm{Ti} \rightleftharpoons (+)\text{-}\mathbf{1}\,(+)\text{-}\mathbf{2}\,\mathrm{Ti}_2 \qquad K_3 \gg 1$$

$$(+)\text{-}\mathbf{1}_2\,\mathrm{Ti}_2 + (+)\text{-}\mathbf{2}_2\,\mathrm{Ti}_2 \rightleftharpoons 2\,(+)\text{-}\mathbf{1}(+)\text{-}\mathbf{2}\,\mathrm{Ti}_2$$
$$K_4 = K_3^2/(K_1 \times K_2) \approx 1$$

With this information we reinvestigated the proportions of the complexes formed with the scalemic mixtures. When using diol **1** of 82 and 62% *ee*, respectively, the integrals of the peaks arising from the diastereomeric complexes **3** and **4** corresponded very well with the expected values using an equilibrium constant of 1 (in the first case: found 65% *de*, calculated 67% *de*; and in the second case: found 38% *de*, calculated 39% *de*).

When examining the NLE of the catalytic reductions a fair amount of THF was present in the reaction mixture. The coordinative qualities of THF may significantly alter the composition or structure of the complexes, for example, by shifting the equilibrium towards a monomeric complex. To investigate this, NMR spectra were recorded of solutions with the mixed complex **6**, and an increasing amount of THF was added to the [D_6]benzene solution. The dilution with THF resulted in shift changes, which we interpreted as a result of solvation by THF and not dissociation of the complex. A reduction in the amplitude of the spectra, caused by dilution was of course also noticed. However, the relative intensity of each complex (1:1:1) was not altered. Furthermore, by using the C_6HD_5 residue in [D_6]benzene as an internal standard, we noted that the amount of the complexes was not different from that in [D_6]benzene.

Only a few reports of Ti-NMR spectra have been reported, which are broad and lack detail.[14] Therefore no detailed structural information could be anticipated for our case. However, we recorded a single ^{49}Ti resonance of **3** at δ −850 ppm ($TiCl_4$ was used as external reference), which was very close to the resonance of [Ti(O*i*Pr)$_4$] at δ −856 ppm. As expected, the peak was very broad lacking fine structure and was of low intensity. A more concentrated solution could not be used since **3** separated as an oily phase. Thus, the only information from the ^{49}Ti-NMR spectrum was that the Ti atom in **3** was most likely bound to an alkoholate similar to [Ti(O*i*Pr)$_4$].

In order to shed some light on the possible structures of the Ti-BODOLate complexes, several alternative structures were investigated by density functional theory calculations. In order to reduce the size of the system, and in particular the number of possible conformations, the isopropoxy groups were modeled as methoxy groups. We first investigated the possible homo-chiral dimeric complexes of **2**, as the least demanding ligand.

Following the previous work on dimeric Ti-complexes,[4] we postulated that a symmetric dimer would form as a di-μ-oxo complex, with a central Ti-O-Ti-O ring. There are three different oxygen atoms that could be employed for the μ-oxo bridges: the isopropoxides or either BODOL-oxygen

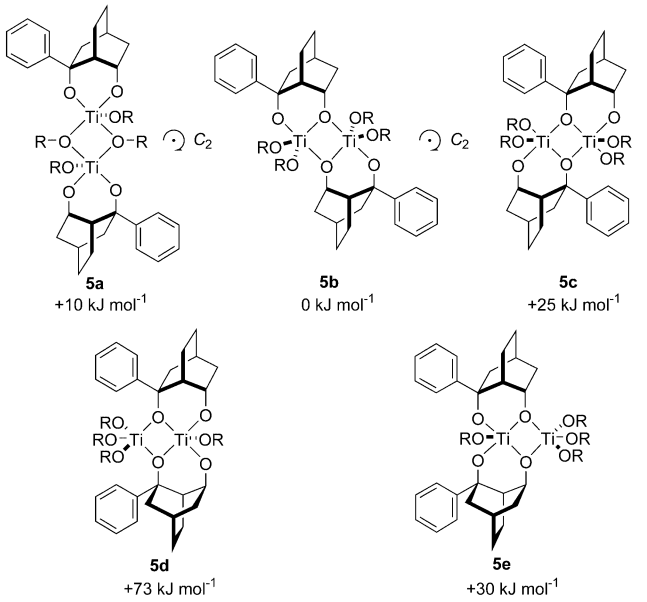

Figure 5. Schematic representation of the C_2-symmetrical head-to-tail complexes **5a**–**c**. The configurations of head-to-head complexes **5d** and **5e** (it should be noted that these complexes lack C_2 symmetry). The computations were performed with OMe, instead of O*i*Pr, to simplify the calculations.

(Figure 5). In the former case, each BODOL unit chelates to one Ti only, with a C_2 axis perpendicular to the core ring (structure **5a**). By forming the μ-oxo using either of the BODOL oxygen atoms allowed the formation of either head-to-tail complexes, with the C_2 axis perpendicular to the core ring (**5b** and **5c**), or head-to-head complexes with the C_2 axis is through the Ti atoms (similar to **5d** and **5e**).

However, with a C_2 axis through the titanium atoms, the alkoxy groups must be distributed with an even number on each Ti, resulting in an unfavorable square-planar conformation for one Ti atom in the head-to-head complexes. To avoid this, the complexes may enter into a tetra-μ-oxo coordination or they can break symmetry by transferring an alkoxy group, resulting in **5d** and **5e**.

However, the complexes resulting from alkoxy transfer (**5d** and **5e**) were investigated, but were found to have fairly high energies and they did not agree with our NMR results (two nonequivalent isopropoxy groups are seen, in a 1:1 ratio, not the 3:1 ratio resulting from alkoxy transfer). The tetra-μ-oxo coordination resulted in very high energies and as we found all of the head-to-head complexes strongly disfavored so that they were not considered any further.

Of the remaining complexes, **5b** (Figure 6) was found to be favored by 10 kJ mol^{-1} over **5a** (Figure 7), and by 25 kJ mol^{-1} over **5c** (Figure 8). The difference is not very large, but higher than the expected errors when comparing with electronically similar complexes. Inspection of the structure of **5b** shows that there is sufficient room to include the isopropoxy groups, and thus validates the use of the computationally less expensive methoxy groups in the modelling studies. Furthermore, it can be clearly seen that the two types of alkoxy groups are in very different environments in **5b**, with one type residing in the anisotropically

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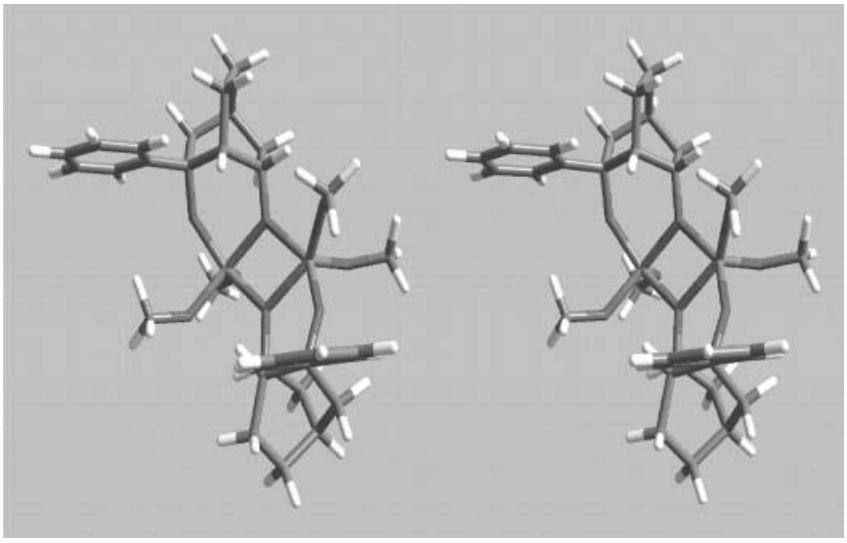

Figure 6. Stereoview representation Ph-BODOL coordinated as complex **5b**, exhibiting the lowest energy conformation, relative energy 0 kJ mol^{-1}. The computations were performed with OMe, instead of O*i*Pr, to simplify the calculations.

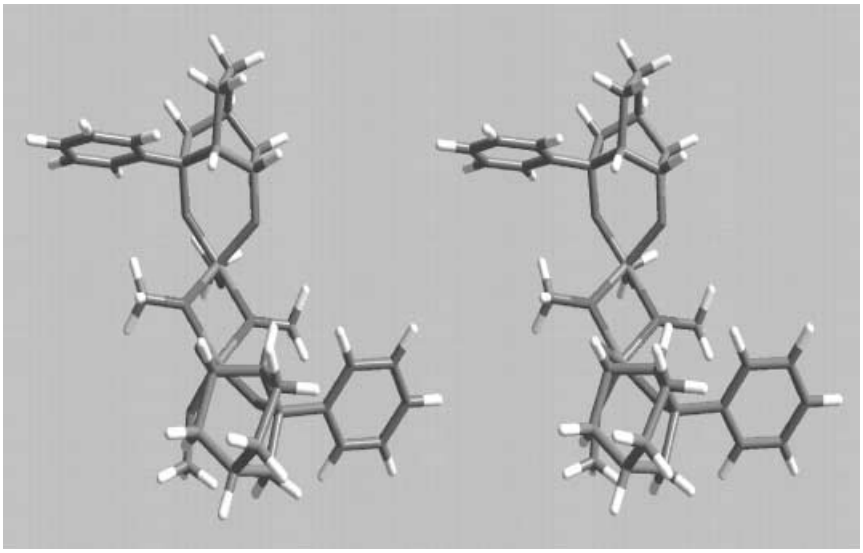

Figure 7. Stereoview representation of Ph-BODOL as the complex **5a**, with the minimized energy conformation at 10 kJ mol^{-1} above complex **5b**. The computations were performed with OMe, instead of O*i*Pr, to simplify the calculations.

shielded region of the phenyl substituent. This fully rationalizes the large shift difference observed for the two types of isopropoxy groups in the dimeric complexes. This feature is also noticed in **5a**, but as the alkoxy groups are more distant from the anisotropy of the phenyl group a smaller effect would be expected. As the effect is substantial this lends further credence to the assignment of **5b** as the structure of the homochiral dimeric complex **7** formed from (±)-**2**.

Starting from complexes **5a–c**, racemic analogues can be obtained by reflecting the asymmetric unit through the center of the Ti-O-Ti-O core, yielding the corresponding C_i-symmetric complexes **7a–c** (Figure 9). These heterochiral complexes are in all respects very similar to, and almost isoenergetic with, their homochiral counterparts **5a–c**. In particular, the most favored racemic complex **7b** was within a few kJ mol^{-1} of **5b**, in very good agreement with the observed statistic distribution for the scalemic complexes. (Due to the loose convergence criteria employed, the exact energy of converged complexes varied by a few kJ mol^{-1} depending on starting structure.) Furthermore, neither of the alkoxy groups of **7a** are anisotopically shielded as they are with **7b**, which additionally support structure **5b** as the best model for the homochiral complexes. However, μ-oxo bridging through the *i*PrO oxygen atoms, as with complexes **5a** and **7a** cannot be ruled out.

The dimeric complexes were found to be favored by 111 kJ mol^{-1}, compared with the free monomer. However, this comparison ignores contributions from solvation and entropy, both of which can shift the equilibrium severely, possibly by up to 100 kJ mol^{-1}. Therefore we can say that the dimeric complexes seem favored energetically, but we cannot estimate the amount of monomeric form reliably. However, the results are certainly in agreement with the experimental observation that only the dimeric forms can be observed in the NMR spectra.

As **5b** exhibited the lowest energy and was almost isoenergetic with its diastereomeric counterpart **7b**, a minimization of the complex **3** was performed with this complex configuration. As can bee seen in the stereoview representation of the minimization (Figure 10) the influence of the OMe located the 2-position of the aromatic ring has a large influence upon the structure of the complex. However, the structures of the ligands themselves are very similar, as seen in Figures 6, 7 and 10; in all cases the dihedral angle of the aromatic ring plane is essentially the same. An interesting factor is that complexation of **3** leads to a restriction of the methoxy substituent in the plane of the phenyl ring, instead of the preferred perpendicular orientation calculated for the free ligand. This transfer into the anisotropic deshielding region fully rationalizes the strong chemical shift change of the methoxy substituent upon complexation.

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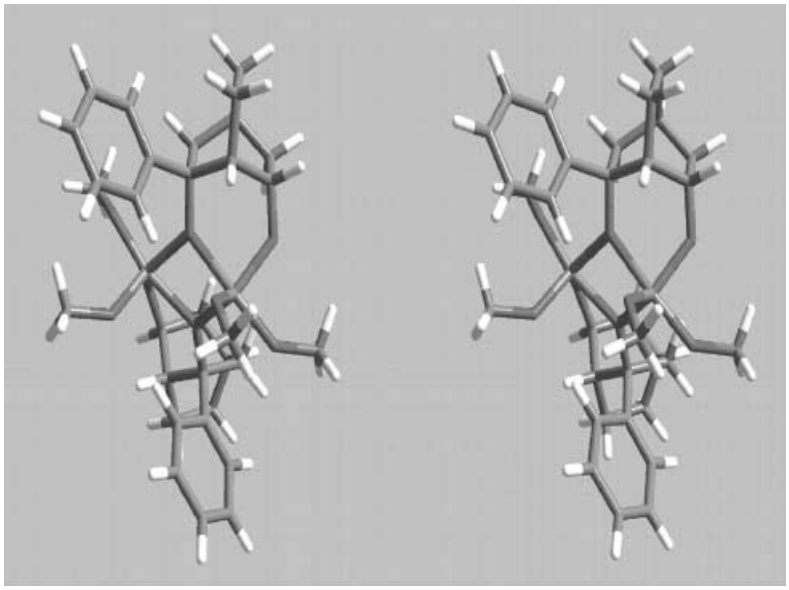

Figure 8. Stereoview representation of Ph-BODOL as the complex **5c**, with the minimized energy conformation at 25 kJ mol^{-1} above complex **5b**. The computations were performed with OMe, instead of O*i*Pr, to simplify the calculations.

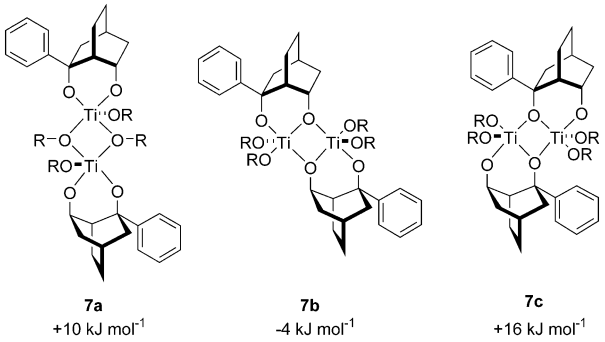

Figure 9. Schematic representation of the C_i-symmetric heterochiral complexes **7a–c**, which are the diastereomeric counterparts to the C_2-symmetrical complexes **5a–c**. The energies displayed are those relative to **5b**. The computations were performed with OMe, instead of O*i*Pr, to simplify the calculations.

Summarizing all available data, we can draw some conclusions about the composition of the observed complex. From the mixing experiments, we know that the complex must contain an even number of ligands, related by symmetry (C_2 or C_i depending on whether the complex is homo- or heterochiral). We also know that we see only one type of complex, and that exchange with any other complex is slow on the NMR time scale, as evidenced by the presence of two isopropoxide signals, and the lack of change in the spectrum in a temperature interval from −65 to +85 °C. The computational data indicate that the best dimers are relatively strain-free. The coordination spheres around the Ti atoms are filled up sterically, but not encumbered. Asssociation to form tetramers would carry an entropic cost of approximately 30 kJ mol^{-1} at room temperature, in addition to an unknown solvation cost. Tetramers or higher oligomers are beyond our current computational resources, but it seems unlikely that these would be so highly favored that the dimers would no longer be visible in the NMR. As additional evidence that the complexes we see are indeed dimers, we see only one heterochiral complex in the scalemic experiments, with the enantiomeric ligands related by symmetry, whereas higher oligomers would be expected to give rise to more complexes, some of which could not possess the required elements of symmetry (homochiral tetramers would by necessity have to have C_4 or D_2 symmetry in order to show only one set of ligand signals).

As a further indication of the dimeric composition of the observed complexes, we have performed molecular weight measurements by the Signer method[15] using benzene as solvent, that is, the same solvent as was used in the NMR measurements. The reliability of this experiment is not high, since decomposition of the ligand occurs during the necessary long equilibration times (several days) at room temperature. However, our best measurements indicate that the molecular weight (ca. 1200) is not lower than for the dimer, and not higher than for the trimer. Since the trimer can be discarded for the reasons mentioned above also these data point toward a dimeric complex. However, these data must be used with caution since in the Signer method all low boiling components such as *i*PrOH were removed, which creates a different environment for the complex compared with the in situ generated complex used in the NMR measurements and in the catecholborane reductions.

Conclusion

The Ti-BODOLates seems to prefer a dimeric composition and the enantiomers of the phenyl and *o*-anisyl BODOLs **1** and **2** are equally well accommodated without any measurable change in equilibrium composition as observed for the mixed complex. The complexes are believed to be bis-μ-oxo dimers with one BODOL oxygen acting as a μ-oxo bridge and the other one coordinating only to one Ti. The complex from enantiomerically pure ligand is most likely C_2-symmetric, whereas the corresponding complex from the racemic ligand displays C_i symmetry. The isopropoxy groups occupy two unequal positions, one of which is strongly shielded by the anisotropy of the aryl substituent, leading to a large chemical shift difference between the resonances of the two isopropoxy groups. Exchange between these positions is slow on the NMR time scale and thus indicate that equilibration with the monomeric complex is also slow. Taken together, the results support that the NLE observed in the cat-

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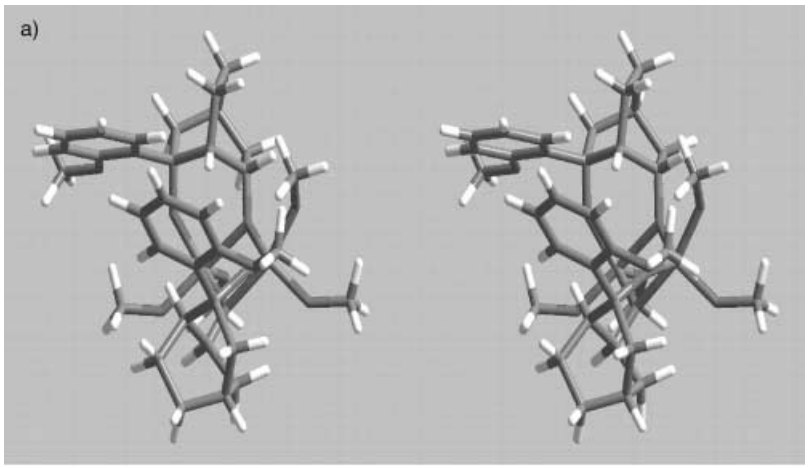
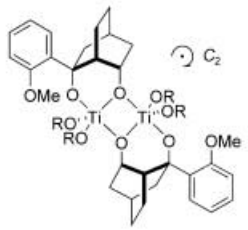


b)



3

Figure 10. Complex **3**: stereoview representation (a) and the schematic representation (b).

echolborane reduction of acetophenone is due to unequal reactivity of the homochiral and heterochiral dimeric complexes, and not to different equilibria with a catalytically active monomeric form. In fact, coordination of acetophenone to the monomeric titanate was highly unfavorable in contrast to coordination to the dimer **5a**, as preliminary computations have indicated. These results will be examined further in due course.

Experimental Section

BODOLs (+)-**1**, (+)-**2** and (±)-**1** were synthesized according to previously published methods.[9] [D_8]Toluene, [D_6]benzene and [D_8]THF were purchased from Dr. Glaser AG Basel and dried over 4 Å molecular sieves before use. [Ti(O*i*Pr)$_4$] was purchased from Aldrich and used as delivered. All ^{1}H NMR data were recorded on a Bruker DRX 400 MHz spectrometer, and the chemical shifts were measured using the solvents as internal references {$CHCl_3$ (^{1}H, 7.27 ppm), $CDCl_3$ (^{13}C, 77.23 ppm), C_6D_5H (^{1}H, 7.16 ppm), C_6D_6 (^{13}C, 128.39 ppm)}. To record the ^{1}H NMR spectra of the complexes the components were mixed directly in the NMR tube, using microsyringes under an argon atmosphere, employing 1.0 M stock solutions of the ligands and 5.0 M stock solutions of [Ti(O*i*Pr)$_4$]. The scalemic mixtures of **1** were prepared by mixing (+)-**1** and (±)-**1**; the *ee* values were determined by chiral phase HPLC Chiralcel OD-H (Daicel) 250×4.6 mm, RT, flow rate; 0.5 mL min^{-1}, detection at 245 nm. Solvent: hexane/*i*PrOH 20:80: t_R = 13 min (1*S*,2*S*,4*R*,6*R*), 17 min (1*R*,2*R*,4*S*,6*S*).

The ^{49}Ti NMR data were collected on a 45 % *w*/*v* solution of **3** in C_6D_6 using a Bruker DRX 500 MHz spectrometer, and the chemical shifts were measured relative to external $TiCl_4$, (80 % *v*/*v*) in $CDCl_3$.

Computational details: All Ti complexes were optimized at the BP86/LACVP* level of theory[16] in Jaguar ver. 4.1 from Schrödinger, Inc.,[17] employing the "accurate" setting for wavefunction convergence and default setting for convergence of the geometries. Following the NMR results, dimeric complexes were optimized in C_2- or C_i symmetry for the homochiral and racemic complexes, respectively.

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