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Insight into the Mechanism of the Asymmetric Addition of Alkyl Groups to Aldehydes Catalyzed by Titanium−BINOLate Species

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Abstract: The asymmetric addition of alkyl groups to aldehydes catalyzed by BINOLate−titanium complexes has become the testing grounds to evaluate the potential of new BINOL-based ligands. We have investigated the mechanism of this reaction and report our findings here. Model systems for the open form of the catalyst, (BINOLate)[Ti(O-*i*-Pr)$_3$]$_2$, based on mono-oxygen-alkylated BINOL ligands have been examined. Comparison of the reactivity and enantioselectivity of the mono-alkyl BINOL derivatives with those of BINOL indicate that the open form of the catalyst, (BINOLate)[Ti(O-*i*-Pr)$_3$]$_2$, is not active in the asymmetric addition reaction. Several BINOLate−titanium complexes have been synthesized and characterized by X-ray crystallography. These include the dinuclear (BINOLate)Ti(O-*i*-Pr)$_2$·Ti(O-*i*-Pr)$_4$, which contains a bridging naphtholate and isopropoxy group, trinuclear (BINOLate)Ti(O-*i*-Pr)$_2$·[Ti(O-*i*-Pr)$_4$]$_2$, and trimeric [(BINOL)Ti(O-*i*-Pr)$_2$]$_3$. The solid-state and solution structures reported here indicate that (BINOLate)Ti(O-*i*-Pr)$_2$ prefers to bind to titanium tetraisopropoxide rather than to itself, explaining why no nonlinear effects are observed in the catalytic reaction. Additionally, experimental evidence suggests that the BINOLate−titanium species responsible for the catalytic and stoichiometric asymmetric addition reactions are different, indicating that the proposed intermediate, (BINOLate)Ti(R)(aldehyde)(O-*i*-Pr), is not involved in either of these processes. Reactions were examined using different sources of the alkyl group [ZnMe$_2$ or MeTi(O-*i*-Pr)$_3$]. Under similar conditions, it was found that the product ee's were the same, independent of whether ZnMe$_2$ or Me-Ti(O-*i*-Pr)$_3$ was used as the source of the alkyl groups. This indicates that the role of the dialkylzinc is not to add the alkyl group to the carbonyl but rather to transfer the alkyl group to titanium. On the basis of these results, we hypothesize that the intermediate in the asymmetric addition involves (BINOLate)Ti(O-*i*-Pr)$_2$(aldehyde)·MeTi(O-*i*-Pr)$_3$.

Introduction

The number of chiral ligands developed for use in asymmetric catalysis has grown rapidly since the 1980s. Of the multitude of ligands that have been used, only a limited number have been successfully applied across a wide range of catalytic asymmetric transformations. One of these ligands is the axially chiral 1,1-bi-2-naphthol (BINOL),[1−4] **1** Figure 1, which has been shown to form highly enantioselective catalysts with main group elements,[1,5] transition metals,[1] f-block elements,[6] and hetero-bimetallic combinations from these groups.[1,2,7−9]

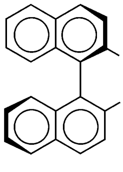

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Figure 1.

The initial choice of metal to be used with BINOL is often based on the ease of generation of the catalyst and the availability of metal-containing precursors. Titanium has been used extensively with BINOL because the catalysts are easily generated in situ and the starting materials are commercially available and inexpensive. Additionally, titanium forms strong bonds to oxygen, resulting in stabilization of the (BINOLate)−titanium moiety. The Lewis acidity of these (BINOLate)TiX$_2$ complexes can be easily tuned by variation of the electronic properties of the X ligands.

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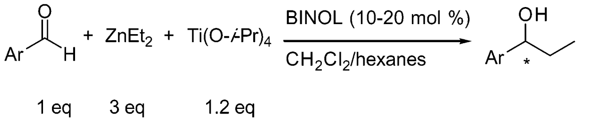
Intense research efforts employing (BINOLate)TiX_2 catalysts have resulted in development of an impressive number of highly enantioselective processes,[1−5,7] including the cyanosylation of aldehydes,[10] Diels−Alder cycloadditions,[11−13] hetero Diels−Alder cycloaddition,[14−16] carbonyl−ene reaction,[17−20] Mukaiyama aldol condensation,[21,22] nitro−aldol condensation,[7,23,24] allylation of aldehydes[25−33] and ketones,[34,35] asymmetric sulfide oxidation,[36] and asymmetric addition of alkyl groups to aldehydes, to name a few.[37−40] Despite the remarkable versatility and enantioselectivity of the titanium−BINOL-derived catalysts, investigations into the structure of these species and their reaction mechanisms have been scarce. The very features that make the titanium−BINOL and related titanium−diol systems[41,42] efficient catalysts, such as the kinetic lability of titanium alkoxide ligands and the Lewis acidic nature of the titanium center, also complicate mechanistic studies. Although it is tempting to represent these catalysts simply as (BINOLate)-TiX_2 species, little experimental evidence has been presented to support these assertions. Indeed, much of the chemistry which was attributed for many years to (BINOLate)TiX_2 (X = halide, alkoxide) complexes[12,17,18,43−45] is now believed to be due to oligomeric (BINOLate)−titanium−oxo species.[12,46−48] The source of the oxo ligand, water, is thought to be the molecular sieves that are necessary for formation of highly enantioselective catalysts.[12] The identity of these efficient and enantioselective catalysts remains elusive.

We are attracted to the study of titanium−BINOL complexes because of the importance of this combination in asymmetric catalysis and the lack of structure/reactivity and structure/enantioselectivity studies. Our initial interest was in the asymmetric addition of alkyl groups to aldehydes catalyzed by titanium−BINOL complexes (eq 1).



(1)

In the absence of titanium tetraisopropoxide, BINOL, or other suitable catalyst, it is known that the transfer of alkyl groups from dialkylzinc reagents to aldehydes is very slow.[40] Many types of ligands,[49] most notably amino alcohols,[50−54] have been shown to accelerate the asymmetric addition reaction.[55,56] However, in the case of BINOL, addition of diethylzinc to aldehydes in the absence of additives resulted in low turnover frequencies (TOFs) and poor enantioselectivities.[40]

Previous studies on the asymmetric addition of alkyl groups to aldehydes have shown that use of a titanium tetraisopropoxide "cocatalyst", in combination with dialkylzinc reagents and chiral ligands, can result in the formation of highly enantioselective catalysts. Yoshioka, Ohno, and Kobayashi have developed bis(sulfonamide) ligands[57,58] that have been applied extensively by Knochel.[59−63] Seebach has introduced TADDOL diol ligands that form very enantioselective catalysts when combined with the appropriate titanium precursors.[64,65] Both of these classes of ligands exhibit poor enantioselectivities and TOFs when employed in the asymmetric addition reaction in the absence of titanium tetraisopropoxide. However, in the presence of titanium tetraisopropoxide, the alcohol product is generated efficiently and with high enantioselectivity. Experimental results

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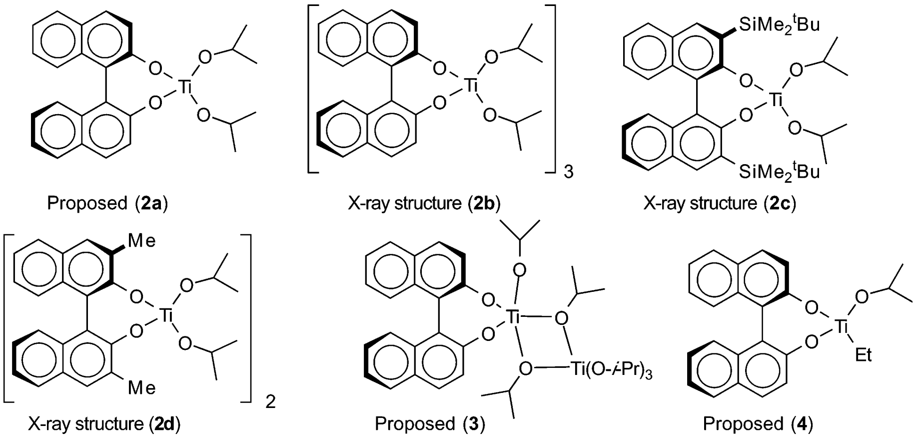

Proposed (**2a**) X-ray structure (**2b**) X-ray structure (**2c**)

X-ray structure (**2d**) Proposed (**3**) Proposed (**4**)

Figure 2. Proposed catalysts for eq 1 and related compounds.

suggest that chiral bis(sulfonamide) ligands and TADDOL ligands are bonded to titanium in these systems.[57,58,64−66] The high enantioselectivity of the catalysts generated from titanium tetraisopropoxide and TADDOL or bis(sulfonamide) ligands inspired the groups of Chan[38] and Nakai[37] to independently employ titanium tetraisopropoxide with the BINOL/diethylzinc system. The BINOLate−titanium complex that resulted proved to be a very enantioselective catalyst in the asymmetric addition of alkyl groups to aldehydes.[37,38] Subsequently, the titanium tetraisopropoxide/diethylzinc system has been examined with partially hydrogenated BINOLs,[67,68] modified[69,70] and hetero-substituted BINOL analogues,[71] fluorinated BINOL derivatives,[36] dendrimers containing BINOL,[72−74] poly-BINOLs,[75−77] polymer-supported BINOL,[78−81] and even fluorous BINOL derivatives in organic/fluorous biphasic systems.[82,83] *This reaction is the primary testing grounds for new BINOL-based ligands to evaluate their utility in asymmetric catalysis.* A more in-depth understanding of this reaction is necessary to better interpret the results from these experiments.

Given the extensive application of the BINOLate−titanium-catalyzed asymmetric addition reactions, it is surprising that little is known about the mechanism of this process. This may be due to the challenging nature of this system, which involves a complex multicomponent reaction where titanium complexes alone play several roles. Proposed intermediates in this reaction include monomeric (BINOLate)Ti(O-*i*-Pr)$_2$, **2a**,[38] while a second report suggests that a dinuclear (BINOLate)Ti(O-*i*-Pr)$_2$Ti(O-*i*-Pr)$_4$, **3**, reacts with diethylzinc to give (BINOLate)Ti(O-*i*-Pr)(Et), **4** (Figure 2).[37] There is little or no experimental evidence for the intermediacy of these compounds.

In work relevant to this study, Sharpless and Martin reported that the solid-state structure of "(BINOLate)Ti(O-*i*-Pr)$_2$" is trimeric, with one six-coordinate and two five-coordinate titanium centers, which will be discussed below.[84,85] This species is reported to be dimeric in solution.[84] Evidence against the intermediacy of the trimeric [(BINOLate)Ti(O-*i*-Pr)$_2$]$_3$, as well as dimeric species, in the asymmetric addition reaction in eq 1 has been presented. Nakai and Mori have reported that the addition reaction (eq 1) exhibits no nonlinear effects,[86] suggesting that it is unlikely that aggregates of (BINOLate)Ti(O-*i*-Pr)$_2$ are involved in the reaction. To rationalize the disparity between the solid-state structure and the solution behavior, and to explain their observation of a complex with a ratio of BINOLate:Ti:isopropoxy of 1:2:6 (by ^{1}H NMR), they proposed a binuclear structure consisting of (BINOLate)Ti(O-*i*-Pr)$_2$ bound to Ti(O-*i*-Pr)$_4$ through bridging isopropoxide groups (**3**, Figure 2). The solid-state structure of this complex is slightly different than the proposed structure, as will be shown below.

Detailed solution and solid-state studies of the interaction of substituted BINOL derivatives with titanium tetraisopropoxide that are relevant to these investigations have been reported. Heppert and co-workers found that 3,3′-disubstituted binaphthol (R$_2$-BINOL) produced monomeric (R$_2$-BINOLate)Ti(O-*i*-Pr)$_2$ when R was very large [R = Si(^{t}Bu)Me$_2$] (**2c**, Figure 2).[87] In contrast, when the 3,3′-substituents were methyl, racemic R$_2$-BINOL (R = Me) provided the heterochiral dimer **2d**, with bridging naphthoxy oxygens.[87] Of particular importance to a study of the mechanism of asymmetric addition reactions catalyzed by titanium BINOLate species in eq 1 is that on addition of excess titanium tetraisopropoxide to the monomeric

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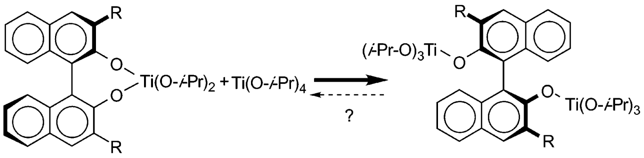
complex (R_2-BINOLate)Ti(O-*i*-Pr)$_2$, **2c** [R = Si(^{t}Bu)Me$_2$], the formation of a complex with a ratio of R_2-BINOLate:Ti: isopropoxy groups of 1:2:6 was observed (eq 2). The structure of this complex (**5c**) was determined by X-ray diffraction and found to contain an open (R_2-BINOLate)[Ti(O-*i*-Pr)$_3$]$_2$, as shown in eq 2. Similar reactivity has been proposed with R_2-BINOL (R = Me) and titanium tetraisopropoxide to give **5d** based on NMR experiments.[87]



2c, R=Si(^{t}Bu)Me$_2$
2d, R=Me (Dimeric)
5c, R=Si(^{t}Bu)Me$_2$
5d, R=Me (2)

The formation of the open (R_2-BINOLate)[Ti(O-*i*-Pr)$_3$]$_2$, **5c**, from 1 equiv of each of **2c** and titanium tetraisopropoxide raises an intriguing question concerning the catalyst in eq 1. Are the dinuclear open forms of BINOLate the catalysts or possibly the catalyst resting state? In the asymmetric addition reaction (eq 1), the ratio of BINOL:Ti(O-*i*-Pr)$_4$ is 1:6. Six equivalents of titanium tetraisopropoxide may give rise to the open form when R = H.

In this work, we have performed experiments designed to shed light on the nature of the catalyst in the asymmetric addition of alkyl groups to aldehydes catalyzed by (BINOLate)−titanium complexes. Model systems of potential intermediates have been developed and structure/reactivity and structure/enantioselectivity relationships have been performed. Additionally, the structures of several titanium−(BINOLate) complexes have been determined that allude to the complicated behavior of "(BINOLate)Ti(O-*i*-Pr)$_2$" in the presence of excess titanium tetraisopropoxide. We also address the role of the dialkylzinc reagent and definitively show for the first time that the titanium and not the zinc transfers the alkyl group to the carbonyl carbon. A portion of this work has been communicated.[85]

Results and Discussion

Possible Catalysts for the Asymmetric Addition of Alkyl Groups to Aldehydes. From the proposed catalysts for eq 1[37,38] and the structural studies of (BINOLate)−titanium complexes[84] and their derivatives,[87] a list of possible titanium catalysts was compiled (Figure 3). This list consists of the open conformation (BINOLate)[Ti(O-*i*-Pr)$_3$]$_2$, which is related to the compounds characterized by X-ray crystallography by Heppert (eq 2).[87] The monomeric (BINOLate)Ti(O-*i*-Pr)$_2$, and the oligomeric forms, which might exist as a dimer, trimer, or higher aggregates, are also included. Although the oligomeric forms have been shown not to be involved in the catalytic process[37] because they exhibited no nonlinear effects[86] (eq 1), the role of these species in the stoichiometric reaction will be investigated. Because titanium alkoxides and titanium−BINOLate derivatives are well known to oligomerize,[87−91] dinuclear species of the type (BINOLate)Ti(O-*i*-Pr)$_2$Ti(O-*i*-Pr)$_4$ must also be included as possible catalysts. The potential catalysts contain four- or five-coordinate titanium and therefore have open coordination sites that can accommodate an additional dative ligand, such as the aldehyde substrate.

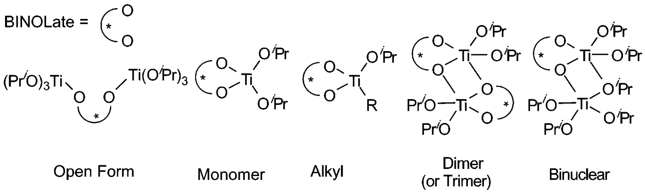
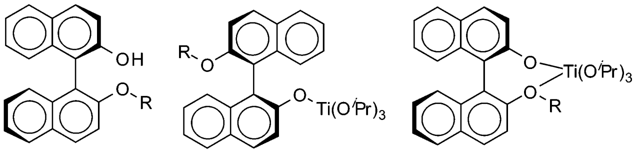


Figure 3. Possible intermediates in the asymmetric addition of alkyl groups to aldehydes (eq 1).

Development of a Model for the Open Form of Titanium−BINOL Complexes. As outlined in the Introduction, in the presence of excess titanium tetraisopropoxide, R_2-BINOL derivatives **2c**,**d** have been shown to react to form (R_2-BINOLate)[Ti(O-*i*-Pr)$_3$]$_2$ (eq 2). Our initial assumption was that if the open form, (BINOLate)[Ti(O-*i*-Pr)$_3$]$_2$, was catalytically active, then the two titanium centers would act independently. On the basis of Heppert's results in eq 2,[87] it is conceivable that dinuclear (BINOLate)[Ti(O-*i*-Pr)$_3$]$_2$ (**5a**) is in equilibrium with titanium tetraisopropoxide and (BINOLate)Ti(O-*i*-Pr)$_2$ (**2a**) under the conditions of the asymmetric addition to aldehydes in eq 1. The equilibrium described in eq 2 could complicate attempts to probe the activity of the open form **5a**. A model for the open form of the ligand, (BINOLate)[Ti(O-*i*-Pr)$_3$]$_2$ (**5a**), was therefore designed to avoid difficulties associated with equilibration between these species (eq 2). To restrict the BINOL ligand to an open conformation, one of the BINOL oxygens was alkylated (Figure 4). The alkyl group (R) serves as a surrogate for one of the Ti(O-*i*-Pr)$_3$ moieties in dinuclear (BINOLate)[Ti(O-*i*-Pr)$_3$]$_2$. We were concerned that the monoalkylated BINOL derivatives **6a**−**c** might behave as bidentate ligands, bonding to the Lewis acidic titanium through both the naphtholate and ether oxygens, giving seven-membered metallocycles (Figure 4). To decrease the likelihood of this chelation, R groups of various sizes were incorporated into the ligands **6a**−**c**. Larger OR groups, such as the O^{t}Bu group of **6c**, are unlikely to coordinate to the titanium center.



6a, R=Me
6b, R=^{i}Pr
6c, R=^{t}Bu

Figure 4. Monoalkylated BINOL ligands **6a**−**c** and their possible bonding modes to titanium.

Synthesis of Open Conformation Model Ligands. The monoalkylation of BINOL was very clean when performed with the alcohol ROH under Mitsunobu conditions as previously reported.[92] The yields were high, except in the case where R =

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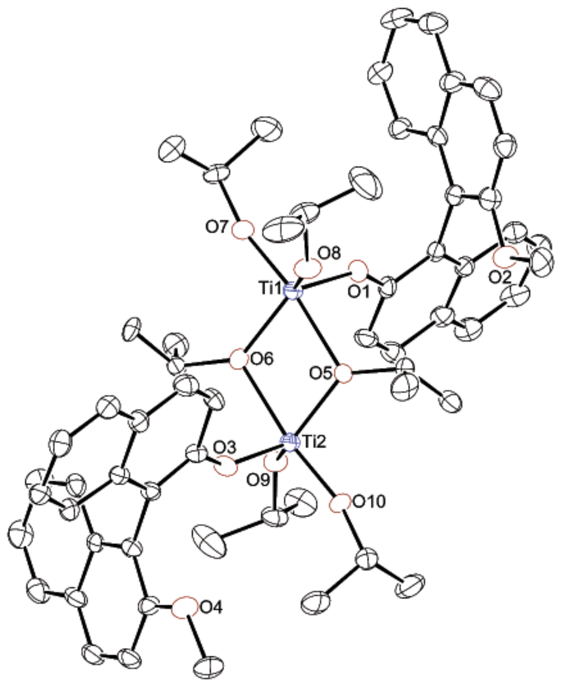
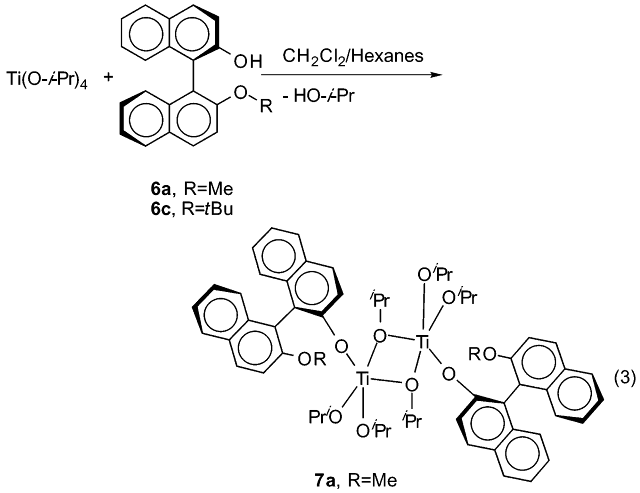


Figure 5. Thermal ellipsoid plot of **7a**. Ellipsoids are at the 30% probability level. Selected bond distances and angles are found in Tables 1 and 2.

^{t}Bu, where only 16% yield of the product was isolated and the unreacted BINOL was recovered. No loss of optical activity of the recovered BINOL was detected (chiral stationary phase HPLC).

Synthesis and Structure of Titanium Complexes of Monoalkylated Ligands. To address the structure and bonding of titanium complexes of monoalkylated ligands **6a**−**c**, the synthesis and structures of these compounds were pursued. Reaction of titanium tetraisopropoxide with ligands **6a**,**c** (eq 3), followed by removal of the volatile materials and crystallization from diethyl ether at −20 °C, provided X-ray quality crystals of **7a**,**c**. The structure determinations of these compounds were performed at low temperature.



6a, R=Me
6c, R=tBu

7a, R=Me
7c, R=tBu

As shown in eq 3 and in the ORTEP diagrams in Figures 5 and 6, both structures consist of dimeric five-coordinate titanium complexes. Bond distances and bond angles are presented in Tables 1 and 2, respectively. Crystal data and collection parameters for all X-ray structures are given in the Supporting Information. In both structures, the titanium atoms have distorted trigonal bipyramidal geometries with the bond angles and bond distances inside the normal range.[87,93,94] Each bridging isopropoxide group is apical with respect to one titanium center and equatorial with respect to the other, resulting in alteration of the Ti−O distances of the dimeric core. In the core, the bridging axial Ti−O distances are approximately 0.2 Å longer than the bridging equatorial Ti−O distances, while the nonbridging isopropoxide Ti−O distances are on the order of 0.05 Å shorter than the naphthylate Ti−O distances.

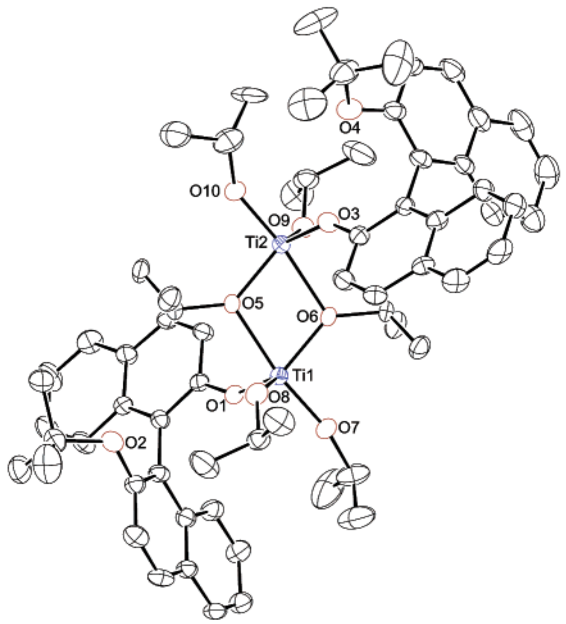


Figure 6. Thermal ellipsoid plot of **7c**. Ellipsoids are at the 30% probability level. Selected bond distances and angles are found in Tables 1 and 2.

Table 1. Selected Bond Distances for **7a** and **7c** (Å)

	7a	7c		7a	7c
Ti(1)−O(7)	1.769(5)	1.770(4)	Ti(2)−O(9)	1.808(4)	1.793(4)
Ti(1)−O(8)	1.792(5)	1.797(5)	Ti(2)−O(3)	1.849(5)	1.846(4)
Ti(1)−O(1)	1.849(4)	1.840(4)	Ti(2)−O(5)	1.917(4)	1.914(4)
Ti(1)−O(6)	1.909(4)	1.915(4)	Ti(2)−O(6)	2.153(4)	2.145(4)
Ti(1)−O(5)	2.153(4)	2.147(4)	Ti(1)−Ti(2)	3.2979(8)	3.270(2)
Ti(2)−O(10)	1.763(4)	1.775(4)			

Table 2. Selected Bond Angles for **7a** and **7c** (Degrees)

	7a	7c		7a	7c
O7−Ti1−O8	99.2(2)	99.3(2)	O10−Ti2−O3	96.5(2)	93.7(2)
O7−Ti1−O1	97.7(2)	95.6(2)	O9−Ti2−O3	112.1(2)	114.0(2)
O8−Ti1−O1	112.2(2)	116.7(2)	O10−Ti2−O5	99.7(2)	99.1(2)
O7−Ti1−O6	99.8(2)	98.3(2)	O9−Ti2−O5	116.5(2)	113.6(2)
O8−Ti1−O6	116.4(2)	113.5(2)	O3−Ti2−O5	124.7(2)	127.3(2)
O1−Ti1−O6	124.3(2)	124.5(2)	O10−Ti2−O6	171.2(2)	170.1(2)
O7−Ti1−O5	171.5(2)	170.1(2)	O9−Ti2−O6	86.1(2)	88.7(2)
O8−Ti1−O5	86.0(2)	88.3(2)	O3−Ti2−O6	87.3(2)	86.9(2)
O1−Ti1−O5	86.5(2)	86.4(2)	O5−Ti2−O6	71.6(2)	72.8(2)
O6−Ti1−O5	71.8(2)	72.8(2)	Ti2−O5−Ti1	108.1(2)	107.1(2)
O10−Ti2−O9	99.7(2)	100.0(2)	Ti1−O6−Ti2	108.4(2)	107.2(2)

Solution Behavior of 7a,c and Their Interaction with Ti(O-*i*-Pr)$_4$. Analysis of the ^{1}H NMR spectra of **7a**,**c** (CDCl$_3$)

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[93] Eilerts, N. W.; Heppert, J. A. *Polyhedron* **1995**, *14*, 3225−3271.

[94] Svetich, G. W.; Voge, A. A. *J. Chem. Soc., Chem. Commun.* **1971**, 676−677.

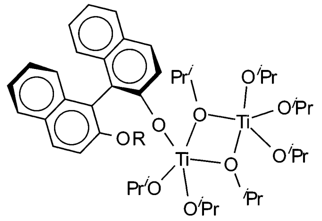
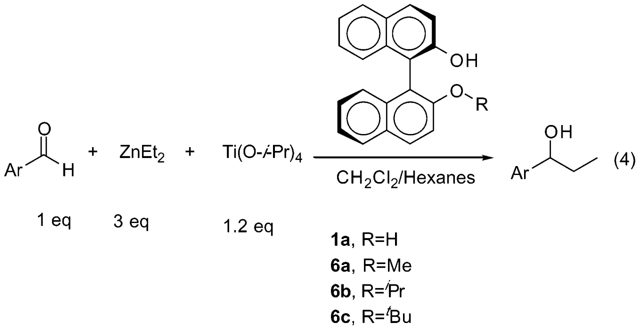


Figure 7. Proposed structure of dinuclear species formed from **7a** or **7c** and Ti(O-*i*-Pr)$_4$.

indicated that, unlike the solid-state structures, two compounds were observed in each case. Although the aromatic region of the ^{1}H NMR spectrum of **7a** was very complex, the methoxy region contained two major resonances at 3.63 and 3.75 ppm that comprised 95% of the signals in this region. The ratio of these resonances was 2:3. Under the conditions of the asymmetric addition reaction, the ratio of titanium tetraisopropoxide to BINOL is 6:1. We therefore added 5 equiv of titanium tetraisopropoxide to the solution of **7a** and analyzed the ^{1}H NMR spectrum. Only a single methoxy resonance was observed at 3.76 ppm. Similarly, the ^{1}H NMR spectrum of **7c** contained two *tert*-butyl resonances at 0.98 and 1.05 ppm in a ratio of 2:3. Addition of 5 equiv of titanium tetraisopropoxide to a solution of **7c** resulted in conversion into a single *tert*-butyl-containing product, with the *tert*-butyl resonance at 1.05 ppm. It is possible that the dimers **7a**,**c** are in equilibrium with the monomeric species in solution. Addition of 5 equiv of titanium tetraisopropoxide may result in the formation of an unsymmetrical dinuclear species consisting of compound **7a** or **7c** bound to a titanium tetraisopropoxide through bridging alkoxides, as shown in Figure 7.

Behavior of Titanium Complexes of Ligands 6a−c under the Conditions of the Asymmetric Addition Reaction. The TOF and enantioselectivity of catalysts derived from the model ligands **6a**−**c** were compared to those of the catalyst formed from BINOL (eq 4). If the ligands **6a**−**c** exhibited ee's and TOFs similar to those of the catalyst formed from BINOL, our conclusion would be that the open form of the catalyst is the active form. Reactions with **6a**−**c** were performed at 20 mol % ligand loading, and BINOL was used at 10 mol %. Additionally, achiral 2-hydroxybiphenyl (**8**) was used as a control in eq 4. This ligand is expected to have steric and electronic properties similar to those of the ligands **6a**−**c** if the ether oxygens of **6a**−**c** do not coordinate to titanium. In this case, the reactivity of the catalyst derived from **8** will be similar to that of **6a**−**c**. However, if the ether oxygens of **6a**−**c** do coordinate, the TOFs of **6a**−**c** will be significantly different than that of the control ligand **8**. The percent conversion and ee of the alcohol product were determined at various points in the reaction by removal of aliquots from the reaction mixtures and analysis of these samples by GC. The results of these experiments are illustrated graphically in Figure 8. Examination of Figure 8 indicates that ligands **6a**−**c** and **8** show very similar conversions over time, providing further evidence that the ether oxygens of **6a**−**c** do not coordinate to the titanium. Comparison of the TOFs and enantioselectivities of catalysts derived from BINOL and **6a**−**c** indicates that the catalyst derived from BINOL is markedly faster than those derived from **6a**−**c**. For example, after 1 h, the reaction conducted with BINOL is 94% complete, while those conducted with **6a**−**c** and **8** range from 13 to 23% complete. Additionally, the enantiomeric excess of the product in the reaction employing BINOL was 89%, while the ee's using ligands **6a**−**c** ranged from −1 to 20%. These results clearly indicate that the active catalyst is not the open form, (BINOLate)[Ti(O-*i*-Pr)$_3$]$_2$.



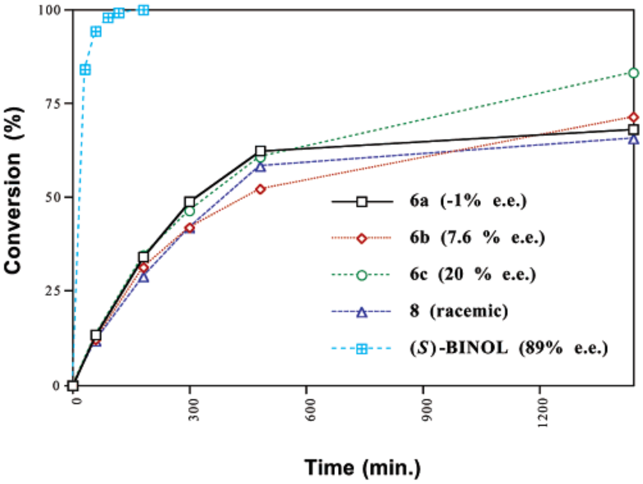


Figure 8. Plot of conversion vs time with ligands **6a**−**c**, **8**, and BINOL (eqs 1 and 4).

BINOL-to-Titanium Ratios of 1:2 and Higher: Structural Studies. Although the open form of the catalyst is not the active catalyst in the asymmetric addition reaction, other BINOLate−titanium complexes with a BINOL-to-titanium ratio of 1:2 must still be considered. Upon combining 6 equiv of titanium tetraisopropoxide with BINOL, Nakai and Mori[37] observed formation of a complex proposed to be (BINOLate)Ti$_2$(O-*i*-Pr)$_6$ (**3**, Figure 2) on the basis of the ^{1}H NMR of this mixture. To address this issue, 2 equiv of titanium tetraisopropoxide was added to 1 equiv of *racemic* BINOL in dichloromethane, and the solvent was evaporated. The resulting solid was redissolved in dichloromethane and cooled to −30 °C. Under these conditions, X-ray quality crystals of **9** formed in 70% yield. The ^{1}H NMR of these crystals indicated that the BINOL-to-isopropoxy ratio was 1:6. Five of the six isopropoxy groups were equivalent on the ^{1}H NMR time scale at room temperature. The ^{13}C{^{1}H} NMR spectrum contains 20 aromatic resonances, indicating that the C_2 symmetry of the BINOL ligand has been lost in **9**. To better understand the bonding in this compound, the structure was determined by X-ray crystallography. Bond distances and bond angles are shown in Tables 3 and 4, respectively. As shown in Figure 9, the structure contains two distinct titanium centers, both of which are significantly distorted from trigonal bipyramidal geometry. The structure differs from the open form of the complex reported by Heppert[87] for (R$_2$-

Table 3. Selected Bond Distances for **9**−**11** (Å)

	9	10	11
Ti(1)−O(1)	2.111(3)	2.147(2)	2.117(2)
Ti(1)−O(2)	1.861(3)	2.156(2)	2.094(2)
Ti(1)−O(3)	1.781(3)	1.779(2)	1.778(2)
Ti(1)−O(4)	1.779(3)	1.778(2)	1.787(2)
Ti(1)−O(5)	1.921(3)	1.999(2)	2.039(2)
Ti(1)−O(9)		1.997(2)	2.082(2)
Ti(2)−O(1)	1.980(3)	2.041(2)	1.996(2)
Ti(2)−O(5)	2.120(3)	2.073(2)	2.116(2)
Ti(2)−O(6)	1.794(3)	1.801(2)	1.857(2)
Ti(2)−O(7)	1.765(3)	1.779(2)	1.781(2)
Ti(2)−O(8)	1.805(3)	1.791(2)	1.773(2)
Ti(3)−O(2)		2.020(2)	2.021(2)
Ti(3)−O(9)		2.087(2)	2.082(2)
Ti(3)−O(10)		1.792(2)	1.851(2)
Ti(3)−O(11)		1.780(2)	1.762(2)
Ti(3)−O(12)		1.794(2)	1.802(2)
Ti(1)−Ti(2)	3.309 (1)	3.348(1)	3.3281(7)
Ti(1)−Ti(3)		3.346(1)	3.3387(7)

Table 4. Selected Bond Angles for **9**−**11** (Degrees)

	9	10	11
O4−Ti1−O3	101.4(2)	103.02(11)	100.53(9)
O4−Ti1−O9		96.33(10)	93.47(9)
O3−Ti1−O9		96.43(10)	97.38(9)
O4−Ti1−O5	114.27(14)	95.95(10)	100.42(9)
O3−Ti1−O5	97.74(13)	95.28(10)	93.14(9)
O9−Ti1−O5		160.66(9)	160.75(8)
O4−Ti1−O1	92.35(13)	92.02(9)	89.10(9)
O3−Ti1−O1	165.32(14)	160.67(10)	162.49(9)
O9−Ti1−O1		93.86(9)	96.58(8)
O5−Ti1−O1	71.69(10)	70.82(8)	70.59(8)
O4−Ti1−O2	110.76(14)	162.07(10)	158.51(9)
O3−Ti1−O2	96.79(13)	90.80(9)	94.72(8)
O9−Ti1−O2		70.48(8)	69.45(7)
O2−Ti1−O5	128.41(12)	94.05(8)	93.72(7)
O2−Ti1−O1	82.78(11)	77.29(7)	80.37(7)
O7−Ti2−O8	100.4(2)	100.88(12)	103.16(12)
O7−Ti2−O6	101.0(2)	97.41(11)	97.42(11)
O6−Ti2−O8	111.5(2)	109.38(12)	107.89(10)
O7−Ti2−O1	91.96(13)	91.46(9)	92.48(10)
O8−Ti2−O1	121.81(13)	110.33(10)	111.52(10)
O6−Ti2−O1	121.51(13)	136.70(10)	135.80(9)
O7−Ti2−O5	162.37(13)	160.64(10)	160.40(10)
O8−Ti2−O5	88.93(13)	93.89(10)	93.36(10)
O6−Ti2−O5	89.22(13)	89.31(10)	87.27(9)
O1−Ti2−O5	70.42(10)	71.55(8)	71.42(8)
O11−Ti3−O10		98.44(12)	98.21(10)
O11−Ti3−O12		101.30(13)	103.92(13)
O10−Ti3−O12		108.35(13)	102.40(11)
O11−Ti3−O2		89.58(10)	90.31(9)
O10−Ti3−O2		132.65(11)	145.01(9)
O12−Ti3−O2		115.66(11)	108.36(10)
O11−Ti3−O9		160.14(11)	151.98(11)
O10−Ti3−O9		90.55(10)	87.13(9)
O12−Ti3−O9		92.50(11)	101.69(10)
O2−Ti3−O9		71.47(8)	70.85(8)
Ti2−O1−Ti1	107.90(11)	106.14(9)	108.00(9)
Ti3−O2−Ti1		106.49(9)	108.43(9)
Ti1−O5−Ti2	109.80(12)	110.63(9)	106.43(9)
Ti1−O9−Ti3		110.06(10)	106.59(9)

BINOLate)[Ti(O-*i*-Pr)$_3$]$_2$ (**5c**, R = $\mathrm{Si}^t\mathrm{BuMe}_2$, eq 2), in that one of the titanium atoms in **9** is interacting with both oxygens of the BINOLate ligand. Additionally, unlike the open form of (R_2-BINOLate)[Ti(O-*i*-Pr)$_3$]$_2$ (**5c**), which exhibits a torsional angle of 98.8° between the two naphthyl groups, the planes defined by these rings in compound **9** have an angle of 54.1°.

From an initial glance at the structure of **9**, it appears as if (BINOLate)Ti(O-*i*-Pr)$_2$ has coordinated to a molecule of Ti(O-*i*-Pr)$_4$. Examination of the Ti−O bond distances, however, indicates that the Ti(2)−O(1) distance [1.980(3) Å] is significantly shorter than the Ti(1)−O(1) distance [2.111(3) Å]. Conversely, the bridging isopropoxy oxygen is interacting more closely with Ti(1) than Ti(2) [Ti(1)−O(5) = 1.921(3) Å, Ti(2)−O(5) = 2.120(3) Å]. The terminal Ti−O distances of the alkoxides are unexceptional and range from 1.779(3) to 1.805(3) Å. As observed for the structures of **7a**,**c**, the Ti−O−C angles in the pseudoaxial alkoxides of **9** [Ti(1)−O(3)−C(21) = 147.2(3)°, Ti(2)−O(7)−C(33) = 165.3(3)°] are significantly larger than the equatorial Ti−O−C angles.

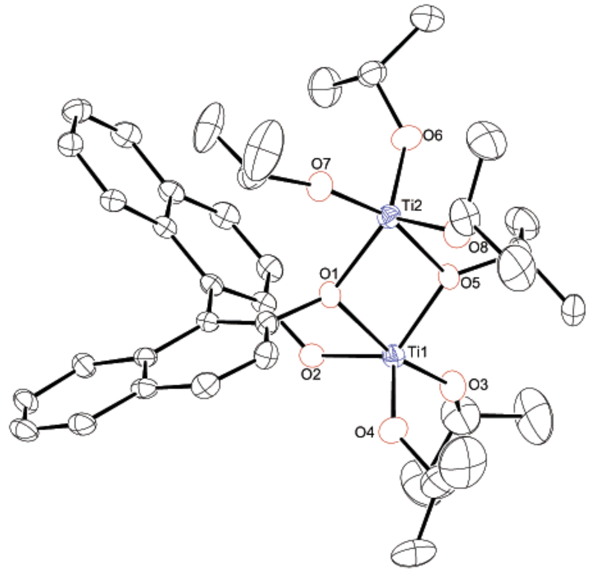


Figure 9. Thermal ellipsoid plot of **9**. Ellipsoids are at the 30% probability level. Selected bond distances and angles are found in Tables 3 and 4.

In the asymmetric addition reaction in eq 1, 120 mol % of titanium tetraisopropoxide and 20 mol % of BINOL are used. We therefore added 6 equiv of titanium tetraisopropoxide to 1 equiv of (*S*)-BINOL. The reaction was stirred for 1 h, and the volatile materials were removed under reduced pressure. Crystallization of the resultant product from pentane at −30 °C gave X-ray quality crystals of **10** (79% yield). The structure of **10** was determined at low temperature, and an ORTEP diagram is illustrated in Figure 10. Selected bond distances and angles are located in Tables 3 and 4, respectively. The structure consists of a trinuclear arrangement of titanium centers bonded to a single BINOLate ligand, as would be expected if **9** were to bind to another titanium tetraisopropoxide. The central titanium is in a pseudo-octahedral environment and bonded to the two naphthylate oxygens as well as two bridging and terminal isopropoxide ligands. The two remaining titanium centers, Ti(2) and Ti(3), are five-coordinate with distorted trigonal-bipyramidal geometries. These titanium centers each contain three terminal isopropoxide groups, a bridging isopropoxide group, and a bridging naphthylate oxygen. The distances of the Ti−O bonds show a pattern similar to those found in **9**. The Ti(1)−O(1) and Ti(1)−O(2) distances [2.147(2) and 2.156(2) Å, respectively] are longer than the Ti(2)−O(1) [2.041(2) Å] and Ti(3)−O(2) [2.020(2) Å] distances, while the Ti(1)−O(5) and Ti(1)−O(9) distances [1.999(2) and 1.997(2) Å, respectively] are shorter than the Ti(2)−O(5) [2.073(2) Å] and Ti(3)−O(9) [2.087(2) Å] distances. The terminal isopropoxide Ti−O distances range from 1.778(2) to 1.802(2) Å.

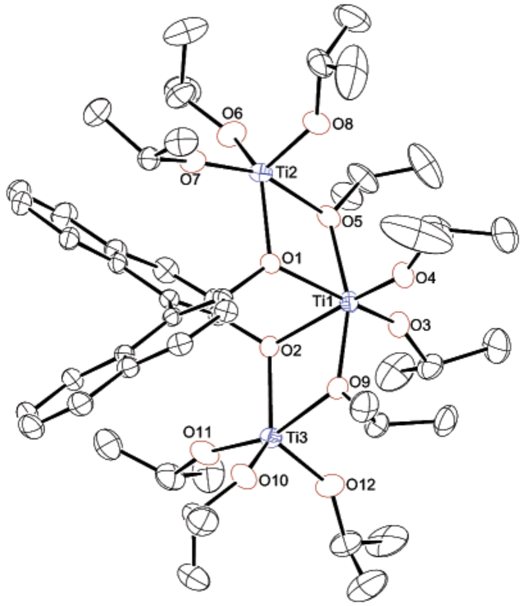


Figure 10. Thermal ellipsoid plot of **10**. Ellipsoids are at the 30% probability level. Selected bond distances and angles are found in Tables 3 and 4.

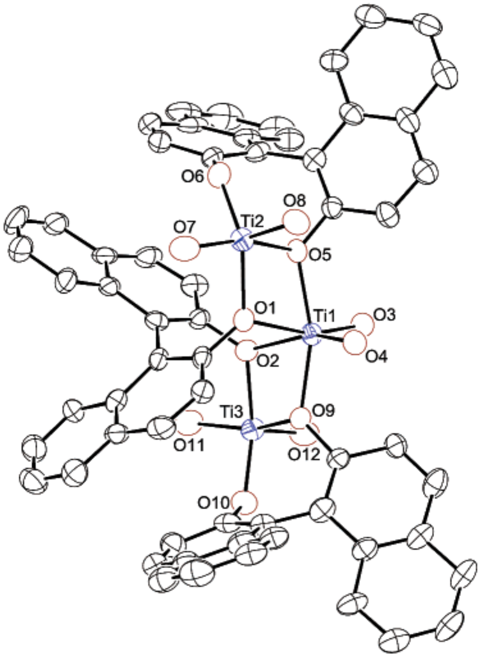


Figure 11. Thermal ellipsoid plot of trimeric **11**. Ellipsoids are at the 30% probability level. The isopropoxy groups have been removed for clarity. Selected bond distances and angles are found in Tables 3 and 4.

Synthesis and Structure of [(BINOL)Ti(O-*i*-Pr)$_2$]$_3$. For the purpose of comparison, crystals were grown from the reaction between titanium tetraisopropoxide and (*S*)-BINOL in a 1:1 ratio by removal of the volatile materials and crystallization of the resulting solid from CH_2Cl_2 at −30 °C. Crystals obtained under these conditions were used in a low-temperature structure determination. The structure is almost identical to a structure reported in the Ph.D. thesis of Dr. C. Martin in the laboratories of Professor K. B. Sharpless.[84] This structure is of significantly higher quality than the trimeric structure we reported earlier.[85] The structure is reported here because the structural determination study is of significantly higher quality than that used for the Martin−Sharpless structure. Importantly, the structure reported by Martin and Sharpless has consistently been incorrectly described.[2,37,95−98] An ORTEP diagram of the structure of **11** with the isopropoxy groups removed for clarity is illustrated in Figure 11. Selected bond distances and bond angles are shown in Tables 3 and 4. The structure is trimeric and is reminiscent of the structure of trinuclear **10** in that one of the titanium centers is in a distorted octahedral geometry, while the remaining titanium centers have distorted trigonal-bipyramidal geometries. Importantly, *only the naphthylate oxygens are bridging the titanium centers, and the isopropoxy groups are all terminal*.

The structures of **9**−**11** provide important insights into the types of complexes that form in the solid state. These complexes must also be considered under the conditions of eq 1. The solid-state structures of **9**−**11** may indicate that the monomer (BINOLate)Ti(O-*i*-Pr)$_2$ is sufficiently Lewis acidic that it does not persist in this form in the presence of titanium alkoxides. Furthermore, the reaction of [(BINOLate)Ti(O-*i*-Pr)$_2$]$_3$ with titanium tetraisopropoxide to give **9** and **10** suggests that (BINOLate)Ti(O-*i*-Pr)$_2$ preferentially coordinates titanium tetraisopropoxide rather than a second molecule of (BINOLate)-Ti(O-*i*-Pr)$_2$. The role of species such as **9** and **10** in the asymmetric addition reaction (eq 1) is unclear at this point. It is improbable that **10** is the active form of the catalyst because the central titanium is six-coordinate and unlikely to further expand its coordination sphere to accommodate the aldehyde substrate. It is more likely that **10** could be a resting state of the catalytically active species. Loss of 1 equiv of titanium tetraisopropoxide from **10** would generate **9**, which has an open coordination site on the titanium chelated by the BINOLate ligand. The ^{1}H and ^{13}C{^{1}H} NMR spectra of **10** show that the complex loses an equivalent of titanium tetraisopropoxide in solution to generate **9**. Experiments designed to probe the role of complex **9** in eq 1 are presented below.

Probing the Effect of Titanium Tetraisopropoxide on Catalyst Behavior. Experiments were designed to further probe the interaction of BINOLate−titanium species with themselves and with titanium tetraisopropoxide. If the active form of the catalyst were the monomeric [(BINOLate)Ti(O-*i*-Pr)$_2$], perhaps generated on loss of titanium tetraisopropoxide from **9**, the enantioselectivity of this species would be the same in the absence and in the presence of titanium tetraisopropoxide. To explore this possibility, reactions were conducted in the absence of titanium tetraisopropoxide using stoichiometric (BINOLate)-Ti(O-*i*-Pr)$_2$. The stoichiometric reactions were also examined with nonenantiopure ligands.

Nonlinear Effects. Examination of the asymmetric addition reaction with BINOL of varying ee in the presence of titanium tetraisopropoxide has been performed by Mori and Nakai.[37] For the purpose of comparison, we have repeated these experiments with 20 mol % of BINOL of 20, 40, 60, 80, and 100% ee in combination with 120 mol % of titanium tetraisopropoxide. Our results match those of Mori and Nakai and are illustrated in

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(95) Harada, T.; Takeuchi, M.; Hatsuda, M.; Ueda, H.; Oku, A. *Tetrahedron: Asymmetry* **1996**, 2479−2482.

(96) Boyle, T. J.; Eilerts, N. W.; Heppert, J. A.; Takusagawa, F. *Organometallics* **1994**, *13*, 2218−2229.

(97) Imma, H.; Mori, M.; Nakai, T. *Synlett* **1996**, 1229−1230.

(98) Kitamoto, D.; Imma, H.; Nakai, T. *Tetrahedron Lett.* **1995**, *36*, 1861−1864.

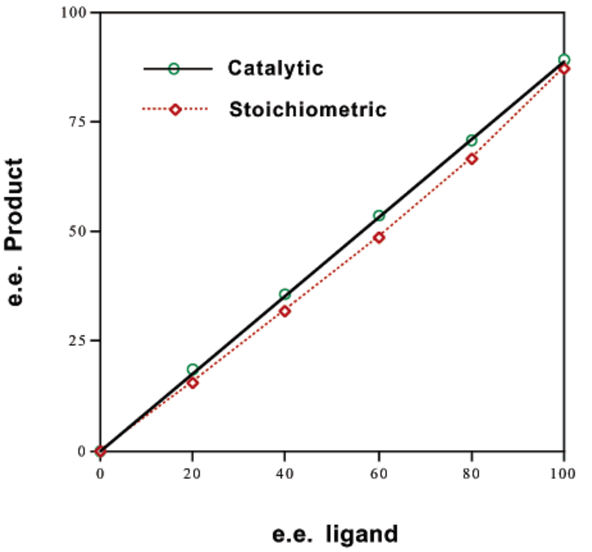
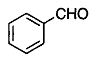
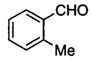
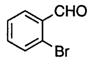
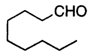
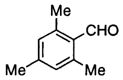
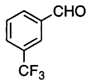
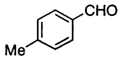


Figure 12. Stoichiometric and catalytic experiments with non-enantiopure BINOL ligand.

Table 5. Comparison of the Product ee's Under Catalytic and Stoichiometric Conditions for Various Adelhydes

Entry	Aldehyde	Alkyl Source	Stoichiometric (ee)[a,b]	Catalytic (ee)[c]	Δee[d]
1		$ZnMe_2$	65.3	50.2	15.1
		$ZnEt_2$	83.7	88.8	-5.1
2		$ZnMe_2$	57.9	18.0	39.9
		$ZnEt_2$	85.2	88.3	-3.1
3		$ZnEt_2$	67.0	66.5	0[a]
4		$ZnEt_2$	88.0	89.0	-1[a]
5		$ZnMe_2$	76.0	-7.8	83.8
		$ZnEt_2$	90.2	78.6	11.6
6		$ZnMe_2$	73.7	59.0	14.7
7		$ZnMe_2$	60.0	44.3	15.7

[a] Ratio of (BINOLate)Ti(O-*i*-Pr)$_2$:aldehyde is 1.00:1.00. [b] The ee's were measured at low conversion to avoid autoinduction. [c] Ratio of (BINOLate)Ti(O-*i*-Pr)$_2$:aldehyde is 0.20:1.00. [d] Δee = stoichiometric ee − catalytic ee.

Figure 12. No nonlinear effects were observed under catalytic conditions. This result can be explained by the preferential formation of the dinuclear species **9** containing a single BINOLate ligand over the oligomeric [(BINOLate)Ti(O-*i*-Pr)$_2$]$_n$, which supports more than one BINOLate. We therefore turned to the stoichiometric reaction with a BINOL-to-titanium tetraisopropoxide ratio of 1:1. Under these conditions, there should be no excess titanium tetraisopropoxide available for bonding to (BINOLate)Ti(O-*i*-Pr)$_2$, and this chiral species will presumably aggregate. Sharpless and Martin have reported that (BINOLate)Ti(O-*i*-Pr)$_2$ is dimeric in solution.[84] Using 100 mol % of BINOL of 20, 40, 60, 80, and 100% ee and 100 mol % of titanium tetraisopropoxide, the asymmetric addition of diethylzinc to benzaldehyde was conducted at 0 °C. The results of these experiments are illustrated in Figure 12. From the graph in Figure 12, a small, but real, negative nonlinear effect can be seen. The observance of nonlinear behavior in the stoichiometric reaction and no nonlinear effect under catalytic reaction conditions supports the assertion that (BINOLate)Ti(O-*i*-Pr)$_2$ preferentially associates with titanium tetraisopropoxide in the catalytic addition reaction (eq 1).

Examination of Different Substrates under Stoichiometric and Catalytic Conditions. In this section, experiments are performed to determine if the (BINOLate)Ti species that promote the stoichiometric and catalytic reactions are the same or different. This will be accomplished by examining the reactivity with different aldehyde substrates and measuring the enantioselectivities under stoichiometric and catalytic conditions. Stoichiometric experiments were performed using 100 mol % of (BINOLate)Ti(O-*i*-Pr)$_2$. Catalytic reactions for these experiments were run with 20 mol % of (BINOLate)Ti(O-*i*-Pr)$_2$ and 80 mol % of titanium tetraisopropoxide.

Five different aldehydes were examined under stoichiometric and catalytic reaction conditions to facilitate the interpretation of the results. The outcome of these experiments is shown in Table 5. Benzaldehyde, nonyl aldehyde, 2-methylbenzaldehyde, and 2-bromobenzaldehyde gave similar results under catalytic and stoichiometric conditions when diethylzinc was used as the source of alkyl groups. These results would suggest that the Lewis acid species promoting the reactions were either closely related or the same. However, when the reactions were run with 2,4,6-trimethylbenzaldehyde, the ee in the catalytic reaction was 79%, while the ee in the stoichiometric reaction was 90%. This observation could be explained if the background reaction promoted by titanium tetraisopropoxide were particularly fast in the catalytic reaction with the more hindered 2,4,6-trimethylbenzaldehyde. The reaction was re-examined using 10, 20, and 30 mol % of catalyst to determine the contribution of the background reaction. The product ee's were 73.3, 78.6, and 79.3%, respectively. From these results, it is apparent that the background reaction was playing a small role when 10 mol % of catalyst was used, but 20 and 30 mol % of catalyst gave the same ee's (within experimental error), indicating that the background reaction was not important at these catalyst loadings. Additionally, the conversions of these reactions were measured after 15 h at 0 °C and found to be 60−77% complete. In contrast, the background reaction, which was run under the same conditions in the absence of BINOL, was only 17% complete after 15 h. Thus, the lower ee of the catalytic reaction is not caused by the background reaction.

We next examined the stoichiometric and catalytic reactions of three of the same aldehydes and two additional aldehydes with dimethylzinc. It is known that dimethylzinc and diethylzinc often give different product ee's with the same catalysts and the same substrates.[99,100] As shown in Table 5, the difference in ee (Δee) between the stoichiometric and the catalytic reactions is significantly larger with dimethylzinc than with diethylzinc. The differences in ee's range from 15% with benzaldehyde and *m*-trifluoromethyl benzaldehyde to 84% with 2,4,6-trimethylbenzaldehyde. In this later case, it is interesting that the catalytic and stoichiometric reactions give product of *opposite configuration*. The results with diethylzinc and dimethylzinc clearly indicate that the Lewis acids promoting the stoichiometric and catalytic reactions are not the same.

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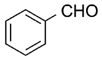
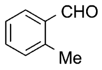
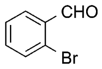
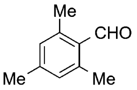
(99) Nowotny, S.; Vettel, S.; Knochel, P. *Tetrahedron Lett.* **1994**, *35*, 4539−4540.

(100) Pu, L.; Yu, H.-B. *Chem. Rev.* **2001**, *101*, 757−824.

Table 6. Effect of Titanium Tetraisopropoxide on the Stoichiometric Reactions with $ZnEt_2$

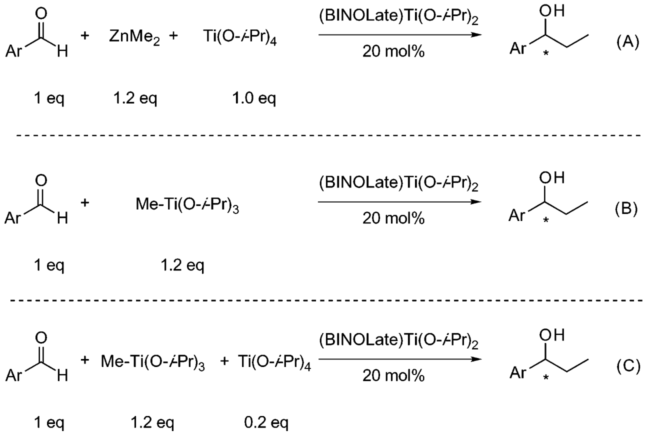
		Stoichiometric[a]			Stoichiometric w/ Ti(O-*i*-Pr)$_4$[b]		
Entry	**Aldehyde**	**Time**	**Conversion**	**ee**	**Time**	**Conversion**	**ee**
1		10 min	50.1%	83.7	10 min	99.2%	89.4
2		10 min	48.8%	85.2	10 min	93.5%	88.7
3		10 min	69.7%	67.0	10 min	98.3%	66.7
4		159 min	49.3%	90.2	159 min	72.6%	82.3

[a] Ratio of (BINOLate)Ti(O-*i*-Pr)$_2$:Ti(O-*i*-Pr)$_4$:ZnEt$_2$:aldehyde is 1.00:0:2.50:1.00. [b] Ratio of (BINOLate)Ti(O-*i*-Pr)$_2$:Ti(O-*i*-Pr)$_4$:ZnEt$_2$:aldehyde is 1.00:1.00:2.50:1.00.

Impact of Titanium Tetraisopropoxide on the Reaction Rates. We attribute the observation that the catalytic and stoichiometric reactions do not give the same enantioselectivities to the presence or absence of titanium tetraisopropoxide. We therefore conducted a series of stoichiometric reactions similar to those outlined above. These reactions were run with 100 mol % of (BINOLate)Ti(O-*i*-Pr)$_2$ (the structure of which is trimeric) and with 100 mol % of titanium tetraisopropoxide. As discussed earlier, the extra equivalent of titanium tetraisopropoxide will bind to (BINOLate)Ti(O-*i*-Pr)$_2$ to give the heterobinuclear complex **9**. The reactions performed with an additional 100 mol % of titanium tetraisopropoxide were run side-by-side with those using only 100 mol % of (BINOLate)Ti(O-*i*-Pr)$_2$ to ensure identical conditions. The results from these experiments indicate that the extra equivalent of titanium tetraisopropoxide caused a substantial rate acceleration and gave the product of slightly different ee. Thus, in the case of benzaldehyde, the reaction with 100 mol % of (BINOLate)Ti(O-*i*-Pr)$_2$ was 50% complete (84% ee), while with 100 mol % of (BINOLate)Ti(O-*i*-Pr)$_2$ and 100 mol % of titanium tetraisopropoxide the reaction was 99% complete (89% ee) in the same period (Table 6). Similar results were observed with 2-methylbenzaldehyde, 2-bromobenzaldehyde, and 2,4,6-trimethylbenzaldehyde. Thus, the titanium tetraisopropoxide alters not only the enantioselectivity of the catalyst but also the rate of the reaction.

Investigation of the Carbonyl Addition Step. A question crucial to understanding the mechanism of the asymmetric addition reaction is that of the role of the dialkylzinc reagent. Is this reagent involved in the C−C bond-forming step? Weber and Seebach have proposed that the role of the dialkylzinc reagent in TADDOLate−titanium-catalyzed addition of dialkylzinc reagents to aldehydes may be to transfer the alkyl group to titanium.[101] This premise was based on similar trends in enantioselectivities when dialkylzinc reagents were used with titanium tetraisopropoxide as compared to use of titanium alkyl species, R-Ti(O-*i*-Pr)$_3$ that were generated in situ from organolithium or Grignard reagents.[101] The asymmetric addition reactions with alkyl group sources ZnR$_2$ and R-Ti(O-*i*-Pr)$_3$ were performed under different conditions by Seebach and coworkers, precluding direct comparison of the enantioselectivities.

Scheme 1. Asymmetric Addition Reactions with $ZnMe_2$ and Me-Ti(O-*i*-Pr)$_3$



We have addressed the issue of the alkyl group transfer by performing three types of experiments (Scheme 1). The first was the simple catalytic addition of dimethylzinc to aldehydes using 20 mol % of (BINOLate)Ti(O-*i*-Pr)$_2$. The second involved the known Me-Ti(O-*i*-Pr)$_3$, which was purified by vacuum distillation. Me-Ti(O-*i*-Pr)$_3$ was substituted for ZnMe$_2$ as the alkyl group source. We employed Me-Ti(O-*i*-Pr)$_3$ (1.2 equiv) with 20 mol % of (BINOLate)Ti(O-*i*-Pr)$_2$. Finally, Me-Ti(O-*i*-Pr)$_3$ (1.2 equiv) was used with 20 mol % of (BINOLate)Ti(O-*i*-Pr)$_2$ and 20 mol % of Ti(O-*i*-Pr)$_4$, as shown in Scheme 1C. Initial experiments with Me-Ti(O-*i*-Pr)$_3$ and benzaldehyde [no added BINOL or (BINOLate)Ti(O-*i*-Pr)$_2$] indicated that the background reaction was extremely fast at 0 °C, consistent with the known chemistry of Me-Ti(O-*i*-Pr)$_3$.[101,102] We were worried that the direct reaction of Me-Ti(O-*i*-Pr)$_3$ with the aldehyde would be too fast, even in the presence of the catalyst, and racemic product would be obtained. However, combination of (BINOLate)Ti(O-*i*-Pr)$_2$, Me-Ti(O-*i*-Pr)$_3$, and benzaldehyde as in Scheme 1B did give moderate enantioselectivity (43% ee). The product ee was lower than that found when dimethylzinc was used in the catalytic reaction (Scheme 1A) (50% ee). We rationalized that the difference in product ee's between the reaction employing ZnMe$_2$ and Me-Ti(O-*i*-Pr)$_3$ might have been due to the rapid background reaction under conditions where a large excess (120 mol %) of Me-Ti(O-*i*-Pr)$_3$ was employed with respect to (BINOLate)Ti(O-*i*-Pr)$_2$ (20 mol %). We therefore performed the reaction with slow addition of Me-Ti(O-*i*-Pr)$_3$ over 30 min at 0 °C with a syringe pump to limit the concentration of Me-Ti(O-*i*-Pr)$_3$ and, therefore, the background reaction with the aldehyde. Under the slow addition conditions, the alkylation of benzaldehyde gave the product with 48.8% ee (vs 50.2% ee for the reaction with ZnMe$_2$, Table 7). We attributed the difference in ee's between reaction with Me-Ti-(O-*i*-Pr)$_3$ and ZnMe$_2$ to autoinduction.[103,104] Autoinduction occurs when the alkoxide product from the asymmetric addition reaction exchanges with an alkoxide in (BINOLate)Ti(O-*i*-Pr)$_2$ to give (BINOLate)Ti(O-*i*-Pr)(OCH(Me)Ph). If (BINOLate)Ti-(O-*i*-Pr)(OCH(Me)Ph) is formed, it will likely promote the asymmetric addition reaction with a different enantioselectivity. To minimize potential problems with incorporation of the

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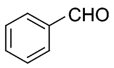
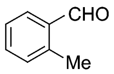
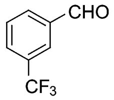
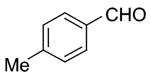
(101) Weber, B.; Seebach, D. *Tetrahedron* **1994**, *50*, 7473−7484.

(102) Reetz, M. T. *Organotitanium Reagents in Organic Synthesis*; Springer-Verlag: Berlin, 1986.

(103) Alberts, A. H.; Wynberg, H. *J. Am. Chem. Soc.* **1989**, *111*, 7265−7266.

(104) Balsells, J.; Costa, A. M.; Walsh, P. J. *Isr. J. Chem.* **2001**, *41*, 251−261.

Table 7. Comparison of the Product ee's with $ZnMe_2$ vs $MeTi(O\text{-}i\text{-}Pr)_3$

Entry	Aldehyde	Alkyl Source	$Ti(O\text{-}i\text{-}Pr)_4$ (mol%)	ee
1		$ZnMe_2$	1.20	50.2[a]
		$Ti(O\text{-}i\text{-}Pr)_3Me$	0.20	50.9[b]
		$Ti(O\text{-}i\text{-}Pr)_3Me$	0	48.8[c]
2		$ZnMe_2$	1.20	18.0[a]
		$Ti(O\text{-}i\text{-}Pr)_3Me$	0.20	18.4[b]
		$Ti(O\text{-}i\text{-}Pr)_3Me$	0	17.2[c]
3		$ZnMe_2$	1.20	59.0[a]
		$Ti(O\text{-}i\text{-}Pr)_3Me$	0.20	59.3[b]
		$Ti(O\text{-}i\text{-}Pr)_3Me$	0	56.7[c]
4		$ZnMe_2$	1.20	44.3[a]
		$Ti(O\text{-}i\text{-}Pr)_3Me$	0.20	43.8[b]
		$Ti(O\text{-}i\text{-}Pr)_3Me$	0	42.0[c]

[a] Ratio of $(BINOLate)Ti(O\text{-}i\text{-}Pr)_2$:$Ti(O\text{-}i\text{-}Pr)_4$:$ZnMe_2$:aldehyde is 0.20:1.20:2.00:1.00. [b] Ratio of $(BINOLate)Ti(O\text{-}i\text{-}Pr)_2$:$Ti(O\text{-}i\text{-}Pr)_4$:$Ti(O\text{-}i\text{-}Pr)_3Me$:aldehyde is 0.20:0.20:1.20:1.00. [c] Ratio of $(BINOLate)Ti(O\text{-}i\text{-}Pr)_2$:$Ti(O\text{-}i\text{-}Pr)_4$:$Ti(O\text{-}i\text{-}Pr)_3Me$:aldehyde is 0.20:0:1.20:1.00.

product alkoxide into the catalyst, reactions were conducted with 20 mol % of $(BINOLate)Ti(O\text{-}i\text{-}Pr)_2$, 120 mol % of $Me\text{-}Ti(O\text{-}i\text{-}Pr)_3$, and an additional 20 mol % of titanium tetraisopropoxide as shown in Scheme 1C. When the reaction was conducted with the extra 20 mol % of titanium tetraisopropoxide, the ee of the product upon addition to benzaldehyde was 50.9%, which is the same as that for the catalytic reaction, within experimental error. Three additional aldehydes, *o*-methyl benzaldehyde, *m*-trifluoromethyl benzaldehyde, and *p*-methyl benzaldehyde, were examined in reactions A−C in Scheme 1, and the results are presented in Table 7. The ee's of the alcohol products were almost identical using these three procedures. These results clearly demonstrate for the first time that *the dialkylzinc reagent is not directly involved in the C−C bond-forming step* because the reactions give the same ee's with a series of aldehydes, but only reaction A in Scheme 1 employs zinc. The role of the dialkylzinc reagent is to transfer the alkyl group to titanium.

Reaction of $Ti(O\text{-}i\text{-}Pr)_4$ and $ZnMe_2$. Having demonstrated that the mechanism of the asymmetric addition with $ZnMe_2$ involves the intermediacy of $Me\text{-}Ti(O\text{-}i\text{-}Pr)_3$, we then examined the interaction of $Ti(O\text{-}i\text{-}Pr)_4$ and $ZnMe_2$ to generate $Me\text{-}Ti(O\text{-}i\text{-}Pr)_3$ and $MeZn(O\text{-}i\text{-}Pr)$ (which is tetrameric $[MeZn(O\text{-}i\text{-}Pr)]_4$).[105−109] After mixing approximately equal molar amounts of $Ti(O\text{-}i\text{-}Pr)_4$ and $ZnMe_2$ in C_6D_6, the 500 MHz ^1H NMR spectrum was acquired. Resonances for $Ti(O\text{-}i\text{-}Pr)_4$ and $ZnMe_2$ were observed as the predominant species in solution. However, a small singlet at 1.02 ppm matched the NMR spectrum of an authentic sample of $Me\text{-}Ti(O\text{-}i\text{-}Pr)_3$. Additionally, a new singlet at −0.27 ppm (3H), a doublet at 1.17 ppm (6H), and a multiplet at 3.94 ppm (1H) were observed, which corresponded to the resonances of an authentic sample of $[MeZn(O\text{-}i\text{-}Pr)]_4$. By integration of the ^1H NMR spectrum using a one-pulse sequence, it was determined that the amount of $Me\text{-}Ti(O\text{-}i\text{-}Pr)_3$ and $[MeZn(O\text{-}i\text{-}Pr)]_4$ was approximately 2−3% of the total titanium and zinc species present. These amounts did not change appreciably over the course of several days. This series of NMR studies further supports the hypothesis that a titanium alkyl species is present under the reaction conditions and, therefore, likely responsible for the addition of the alkyl group to the aldehyde.

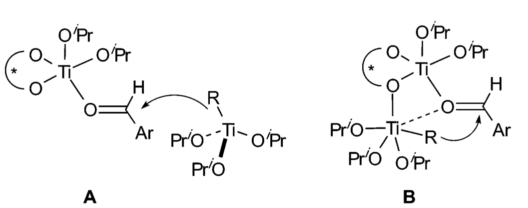


Figure 13. Possible mechanisms for the asymmetric addition step.

Mechanistic Considerations. Analysis of the results from the experiments described above allows several conclusions to be drawn about the mechanism of the asymmetric addition of alkyl groups to aldehydes catalyzed by BINOLate−titanium species. These results indicate that there are two titanium centers involved in the asymmetric addition. If there were a common intermediate of the type $(BINOLate)TiMe(aldehyde)(O\text{-}i\text{-}Pr)$ in the stoichiometric and catalytic reactions, they would give the same enantioselectivities. As shown in Table 5, this is clearly not the case. Furthermore, it is likely that the methyl group is transferred from $(BINOLate)TiMe(O\text{-}i\text{-}Pr)$ in the stoichiometric reactions (in the absence of titanium tetraisopropoxide), but this intermediate is probably not formed in the catalytic addition reactions (no nonlinear effects). It is conceivable that the nonlinear effects in the stoichiometric reaction with no extra titanium tetraisopropoxide arise as a result of the two titanium centers involved in the carbonyl addition step. One metal can activate the aldehyde, and the other delivers the methyl group. Because all the titanium centers bear chiral ligands in the stoichiometric reaction, the two metals involved in the asymmetry-determining step can have either the same configuration of the ligands or the opposite.

Several related mechanisms can be proposed which are consistent with the experimental results outlined here. We presume that the aldehyde is activated by a Lewis acidic titanium complex which also supports the BINOLate ligand. It is also likely that the alkyl group is delivered by an achiral titanium center, consistent with the lack of nonlinear effects in the catalytic asymmetric addition reaction. There are then a spectrum of possible pathways ranging from direct, bimolecular addition of the alkyl group to the aldehyde bound to $(BINOLate)Ti(O\text{-}i\text{-}Pr)_2$ (**A**, Figure 13) to the initial formation of a binuclear complex containing the BINOLate ligand, aldehyde, and alkyl group (**B**). Because of the tendency of the (BINOLate)−titanium complexes to associate, we favor the formation of a binuclear intermediate (**B**), as illustrated in Figure 13.

Summary. Many researchers have used the asymmetric addition of alkyl groups to aldehydes to test new BINOL-based catalysts.[36−38,67−83] The BINOL-catalyzed reaction (eq 1) will continue to serve as the primary testing ground for new BINOL-based ligands. Therefore, it is important to understand the catalyst structure and its mode of action to better evaluate the promise of new BINOL-based ligands. In this study, we have characterized a series of titanium−BINOLate complexes. Their structures represent a significant fraction of the known BINO-

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Late structures with first row transition metals.[110] From these investigations, the propensity of titanium−BINOLate complexes to aggregate is evident.

Extensive solution and reactivity studies have also been performed. Although literature precedence for the formation of dinuclear open forms of titanium−BINOLate complexes, $(R_2\text{-BINOLate})[Ti(O\text{-}i\text{-}Pr)_3]_2$, exists, we have demonstrated that such species do not catalyze the asymmetric addition reaction. In the examination of the enantioselectivity of the catalytic and the stoichiometric asymmetric addition reactions with a series of structurally different aldehydes, it was found that they give alcohol products with different ee's, indicating that the Lewis acids promoting the stoichiometric and catalytic addition reactions are not the same. Based on this result, the active complex for this reaction cannot be the monomeric alkyl complex (BINOLate)TiMe(aldehyde)(O-*i*-Pr). In experiments designed to probe the alkylation step by employing $Me\text{-}Ti(O\text{-}i\text{-}Pr)_3$ as the source of alkyl groups, it was found that the enantioselectivities were identical to those obtained using dimethylzinc under catalytic conditions. These experiments definitively demonstrate that the role of the zinc is to deliver the alkyl group to titanium, which subsequently transfers it to the aldehyde. From the solution structures, reactivity, and solid-state structures, it is clear that the active species involves two titanium centers, one with a BINOLate ligand and the other with an alkyl group. We favor a complex of the type $(BINOLate)Ti(aldehyde)(O\text{-}i\text{-}Pr)_2{\cdot}Ti(O\text{-}i\text{-}Pr)_3Me$, as shown in Figure 13.

Further studies are underway, addressing the role of titanium alkyl species in asymmetric addition reactions with other ligands and examining other (BINOLate)Ti-based catalysts.

Experimental Section

General Considerations. All manipulations involving titanium alkoxides and dialkylzinc reagents were carried out under an inert atmosphere in a Vacuum Atmospheres drybox with attached MO-40 Dritrain, or by using standard Schlenk or vacuum line techniques. Solutions were degassed as follows: they were cooled to −196 °C, evacuated under high vacuum, and thawed. This sequence was repeated three times in each case. ^1H NMR spectra were obtained using the Bruker 200, 360, or 500 MHz Fourier transform NMR spectrometer at the University of Pennsylvania NMR facility. ^1H NMR spectra were recorded relative to tetramethylsilane. $^{13}C\{^1H\}$ NMR spectra were obtained at either 50 or 125 MHz on the 200 or 500 MHz instruments, respectively, and chemical shifts were recorded relative to the solvent resonance. ^1H chemical shifts are reported in units of parts per million downfield from tetramethylsilane, and all coupling constants are reported in hertz. IR spectra were obtained on a Perkin Elmer 1600 series spectrometer. Unless otherwise specified, all reagents were purchased from Aldrich Chemical Co. Titanium tetraisopropoxide and all aldehydes were distilled under vacuum and stored in glass vessels sealed with Teflon stoppers. Diethylzinc (1 M in hexanes) and titanium alkoxide (0.15 M in dichloromethane) solutions were prepared in the drybox and stored in glass vessels sealed with Teflon stoppers. Dimethylzinc (2 M, toluene) was purchased from Aldrich Chemical Co. The titanium complex $Me\text{-}Ti(O\text{-}i\text{-}Pr)_3$ was synthesized by the literature method and distilled under vacuum.[111]

Hexanes (UV grade, alkene-free), dichloromethane, toluene, and diethyl ether were dried using alumnia columns under nitrogen. Deuterated solvents were purchased from Cambridge Isotopes. Benzene-d_6 was vacuum transferred from sodium/benzophenone ketyl under vacuum. $CDCl_3$ was dried over calcium hydride and vacuum transferred.

Synthesis of Monoprotected BINOL Ligands 6a−c. Ligands **6a**,**b** were prepared according to a literature procedure.[92] A modified procedure was used for the preparation of ligand **6c**. A THF solution of (*S*)-BINOL, *tert*-butyl alcohol, DEAD, and triphenyl phosphine was refluxed for 3 days and then worked up according to the procedure of Ogasawara.[92] The yield of **6c** was 16%. Unreacted BINOL was recovered (74%) and its enantiopurity determined to be >99% (HPLC, Chiralpak AS column).

General Procedure for the Alkylation of Benzaldehyde with Diethylzinc, BINOL, and Titanium Isopropoxide. To a solution of (*S*)-BINOL (28.6 mg, 0.1 mmol, 0.2 equiv) in 4 mL of dichloromethane was added titanium isopropoxide (0.24 mL, 0.6 mmol, 1.2 equiv). The resulting yellow solution was cooled to 0 °C, and diethylzinc (1.5 mL, 1.0 M in hexanes, 3 equiv) was added. After 20 min, benzaldehyde was added (52 μL, 0.5 mmol, 1 equiv). Samples were taken from the reaction and quenched with 2 N HCl. The aqueous layer was extracted with pentane, which produced the precipitation of the BINOL. The resulting solution was analyzed by gas chromatography: Supelco SPB-5, 30 m × 0.25 mm; 115 °C, 2.8 mL/min; benzaldehyde, 3.7 min; (*R*)-1-phenyl-1-propanol, 16.0 min; (*S*)-1-phenyl-1-propanol, 16.9 min.

Use of Monoprotected Ligands 6a−c. The above procedure was used for the reactions with ligands **6a**−**c**, 2-phenylphenol, and BINOL.

Linearity Experiments. The appropriate amounts of (*S*)-BINOL and racemic BINOL were combined to give ligand of the desired enantiomeric excess. Reactions were conducted as outlined in the general procedure above.

Use of Recrystallized 2b. The general procedure was used for reactions using **2b** instead of BINOL. The amount of diethylzinc used was 2.6 equiv (relative to aldehyde).

Representative Procedure for Addition of Methyl Groups to Aldehydes Employing $ZnMe_2$. $(BINOLate)Ti(O\text{-}i\text{-}Pr)_2$ (0.089 g, 0.196 mmol) and $Ti(O\text{-}i\text{-}Pr)_4$ (0.336 g, 1.18 mmol) were dissolved in 4 mL of CH_2Cl_2 and introduced into a dry Schlenk flask under nitrogen. The reaction mixture was cooled to 0 °C, and $ZnMe_2$ (2.0 M solution in toluene, 0.98 mL, 1.96 mmol) was added. The reaction was allowed to stir for 15 min, and benzaldehyde (0.10 mL, 0.98 mmol) was added by syringe. Samples from the reaction were taken at different times and quenched by stirring with 2 M $NaHSO_4$. The organic layer was diluted with pentane, and the resulting solution was stored at −20 °C to produce the precipitation of BINOL. Samples were analyzed by gas chromatography: Supelco SPB-5, 30 m × 0.25 mm; 100 °C; 2.8 mL/min; (*R*)-1-phenyl-1-ethanol, 19.3 min; (*S*)-1-phenyl-1-ethanol, 21.2 min.

Representative Procedure for Addition of Methyl Groups to Aldehydes Employing $Me\text{-}Ti(O\text{-}i\text{-}Pr)_3$. $(BINOLate)Ti(O\text{-}i\text{-}Pr)_2$ (0.089 g, 0.196 mmol), $Ti(O\text{-}i\text{-}Pr)_4$ (0.056 g, 0.196 mmol), and benzaldehyde (0.104 g, 0.980 mmol) were dissolved in 2 mL of CH_2Cl_2 and introduced in a dry Schlenk flask under nitrogen. The reaction mixture was cooled to 0 °C. $Me\text{-}Ti(O\text{-}i\text{-}Pr)_3$ (0.284 g, 1.18 mmol) was dissolved in 2 mL of CH_2Cl_2 and added over a 30 min period using a syringe pump. Samples from the reaction were taken at different times and quenched by stirring with 2 M $NaHSO_4$. The organic layer was diluted with pentane, and the resulting solution was stored at −20 °C to produce the precipitation of BINOL. Samples were analyzed by gas chromatography.

Determination of Alcohol Enantiomeric Excesses. Unless otherwise mentioned, samples taken from the reaction were quenched with 2 N HCl. The aqueous layer was extracted with pentane, which caused the precipitation of the ligand. The resulting solutions were analyzed by gas chromatography using a chiral stationary phase column (Supelco SPB-5, 30 m × 0.25 mm). For 1-[2-methylphenyl]-1-propanol: 115 °C, 2.8 mL/min; 2-methylbenzaldehyde, 5.6 min; (*R*)-1-[2-methylphenyl]-1-propanol, 26.6 min; (*S*)-1-[2-methylphenyl]-1-propanol, 30.1 min.

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(110) A search of the Cambridge Crystallographic Database for transition metal complexes of BINOLate derivatives resulted in nine structures, four of which were metallocene-based complexes.

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For 1-[2-bromophenyl]-1-propanol: 140 °C, 2.8 mL/min; 2-bromobenzaldehyde, 5.6 min; (*R*)-1-[2-bromophenyl]-1-propanol, 24.5 min; (*S*)-1-[2-bromophenyl]-1-propanol, 27.0 min. For 1-[2,4,6-trimethylphenyl]-1-propanol: 140 °C, 2.8 mL/min; mesitaldehyde, 5.8 min; (*R*)-1-[2,4,6-trimethylphenyl]-1-propanol, 20.0 min; (*S*)-1-[2,4,6-trimethylphenyl]-1-propanol, 21.9 min. For 3-undecanol, samples taken from the reaction were quenched by stirring over acetic anhydride for 10 min, combined with saturated NH_4Cl, and stirred for 10 min. The aqueous layer was extracted with pentane, which produced the precipitation of the ligand. The resulting solution was analyzed by gas chromatography: 115 °C, 2.8 mL/min; 3-undecanyl acetate, 17.0 min, 18.2 min. For 1-[2-methylphenyl]-1-ethanol: 115 °C, 2.8 mL/min; (*R*)-1-[2-methylphenyl]-1-ethanol, 35 min; (*S*)-1-[2-methylphenyl]-1-ethanol, 37 min. For 1-[4-methylphenyl]-1-ethanol: 115 °C, 2.8 mL/min; (*R*)-1-[4-methylphenyl]-1-ethanol, 13.8 min; (*S*)-1-[4-methylphenyl]-1-ethanol, 15.1 min. Fpr 1-[3-trifluoromethylphenyl]-1-ethanol: 115 °C, 2.8 mL/min; (*R*)-1-[3-trifluoromethylphenyl]-1-ethanol, 9.8 min; (*S*)-1-[3-trifluoromethylphenyl]-1-ethanol, 10.5 min.

Preparation of Titanium Complex 7a. Ligand **6a** (120 mg, 0.4 mmol) was dissolved in 5 mL of diethyl ether, and titanium isopropoxide was added (114 mg, 0.4 mmol). The solution was then cooled to −20 °C, resulting in the formation of crystals (150 mg, 0.29 mmol, 71%) which were used for the crystallographic and solution studies. A mixture of two compounds was observed by NMR. Integration of the CH_3O signals showed a 1.4:1 ratio. The full ^1H NMR and $^{13}C\{^1H\}$ NMR spectra are shown in the Supporting Information. Selected resonances: ^1H NMR ($CDCl_3$, 500 MHz) δ 0.6−1.6 (b, CH_3), 3.63 (s, CH_3O), 3.76 (s, OCH_3), 4.1−4.4 (b, CH), 6.9−8.0 (m, aromatics) ppm. After addition of 5.0 equiv of titanium isopropoxide, only one compound containing **7a** was observed: ^1H NMR ($CDCl_3$, 500 MHz) δ 1.22 (d, $CH(CH_3)_2$), 3.76 (s, OCH_3), 4.46 (sep, $CH(CH_3)_2$), 6.9−8.0 (m, aromatics) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 26.4 (CH_3), 56.8 (OCH_3), 76.3 (OCH), 114.4, 122.1, 122.8, 123.3, 125.5, 125.7, 125.8, 126.0, 127.6, 127.8, 128.7, 128.9, 129.0, 129.4, 134.1, 134.2, 155.2, 159.7 ppm. Two aromatic carbons were not observed. Anal. Calcd for $C_{30}H_{36}O_5Ti$: C, 68.70; H, 6.92. Found: C, 67.96; H, 6.99.

Preparation of Titanium Complex 7c. The procedure for the synthesis of **7c** was identical to that used for the preparation of **7a**. The yield was 51% (92 mg, 0.158 mmol). A mixture of two compounds was observed by NMR. Integration of the $(CH_3)_3C$ signals showed a 1.5:1 ratio. The full ^1H NMR and $^{13}C\{^1H\}$ NMR spectra are shown in the Supporting Information. Selected resonances: ^1H NMR ($CDCl_3$, 500 MHz) δ 0.99 (s, ^{t}Bu), 1.05 (s, ^{t}Bu), 1.0−1.6 (b, CH_3), 4.1−4.4 (b, CH), 6.9−8.0 (m, aromatics) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 29.4 ($C(CH_3)_3$), 29.5 ($C(CH_3)_3$) ppm. After addition of 5.0 equiv of titanium isopropoxide, only one compound was observed: ^1H NMR ($CDCl_3$, 500 MHz) δ 1.05 (s, $C(CH_3)_3$), 1.22 (d, $CH(CH_3)_2$), 4.46 (sep, $CH(CH_3)_2$), 6.9−8.0 (m, aromatics) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 26.4 (CH_3), 29.4 (^{t}Bu), 76.3 (CH−O), 118.7, 122.0, 122.7, 123.9, 125.6, 125.7, 126.3, 126.6, 127.0, 127.5, 127.6, 127.9, 128.6, 128.9, 130.5, 134.2, 152.3, 159.5 ppm. Two aromatic carbons and the quaternary ^{t}Bu carbon were not observed. Anal. Calcd for $C_{33}H_{42}O_5Ti$: C, 69.96; H, 7.47. Found: C, 69.64; H, 7.47.

Preparation of Titanium Complex 9. Racemic BINOL (286 mg, 1.0 mmol) was dissolved in 10 mL of dichloromethane, and titanium isopropoxide (568 mg, 2.0 mmol) was added. The resulting mixture was stirred at room temperature for 30 min. The volatile materials were removed under reduced pressure. Recrystallization of the resulting solid by dissolving it in dichloromethane and cooling to −30 °C yielded X-ray quality crystals of **9**. The yield was 70% (512 mg, 0.7 mmol): ^1H NMR ($CDCl_3$, 500 MHz) δ 1.0−1.3 (m, 36H), 4.51 (b, 6H), 6.75 (b, 1H), 7.1−7.2 (m, 3H), 7.2−7.3 (m, 3H), 7.3−7.4 (m, 1H), 7.47 (d, J = 8.6 Hz, 1H), 7.75 (d, J = 8.8 Hz, 1H), 7.78 (d, J = 8.1 Hz, 1H), 7.86 (d, J = 8.1 Hz, 1H) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 25.4, 25.6, 26.3 (b), 76.3 (b), 81.0, 118.5, 119.4, 121.1, 122.6, 122.8, 123.3, 125.1, 125.4, 126.9, 127.0, 127.8, 128.0, 128.1, 128.8, 129.9, 130.1, 133.1, 133.5, 158.9, 159.9 ppm.

Preparation of Titanium Complex 10. (*S*)-BINOL (516 mg, 1.8 mmol) was dissolved in 10 mL of dichloromethane, and titanium isopropoxide (3.08 g, 10.8 mmol) was added. The resulting mixture was stirred at room temperature for 1 h. The volatile materials were removed at reduced pressure. The solid obtained was recrystallized by dissolving it in pentane and cooling to −30 °C. The yield was 79% (1.45 g, 1.42 mmol). X-ray quality crystals were obtained by dissolving **9** in pentane/dichloromethane (90:10 v/v) and cooling the solution to −30 °C: ^1H NMR ($CDCl_3$, 500 MHz) δ 1.0−1.3 (m, 60H), 4.51 (b, 10H), 6.75 (b, 1H), 7.1−7.2 (m, 3H), 7.2−7.3 (m, 3H), 7.3−7.4 (m, 1H), 7.47 (d, J = 8.6 Hz, 1H), 7.75 (d, J = 8.8 Hz, 1H), 7.78 (d, J = 8.1 Hz, 1H), 7.86 (d, J = 8.1 Hz, 1H) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 25.4, 25.6, 26.3 (b), 76.3 (b), 81.0, 118.5, 119.4, 121.1, 122.6, 122.8, 123.3, 125.1, 125.4, 126.9, 127.0, 127.8, 128.0, 128.1, 128.8, 129.9, 130.1, 133.1, 133.5, 158.9, 159.9 ppm.

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Supporting Information Available: Detailed information on the crystal structure determinations of **7a**,**c** and **9**−**11**, including tables of data collection parameters, final atomic positional and thermal parameters, and interatomic distances and angles as well as ORTEP diagrams; also included are NMR data for **7a**,**c** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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