

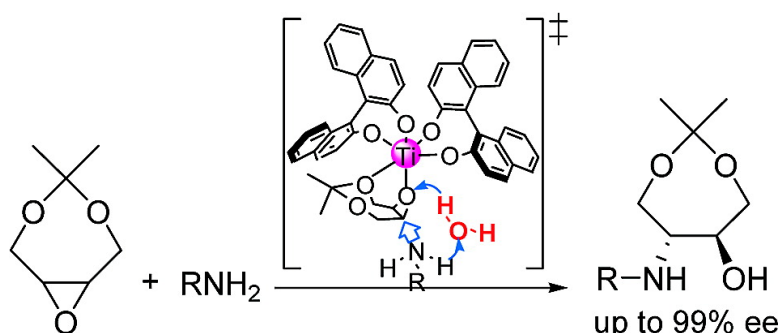
Article

Insight into the Mechanism of the Asymmetric Ring-Opening Aminolysis of 4,4-Dimethyl-3,5,8-trioxabicyclo[5.1.0]octane Catalyzed by Titanium/BINOLate/Water System: Evidence for the Ti(BINOLate)-Bearing Active Catalyst Entities and the Role of Water

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J. Am. Chem. Soc., **2008**, 130 (31), 10116-10127 • DOI: 10.1021/ja801847r • Publication Date (Web): 11 July 2008

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Insight into the Mechanism of the Asymmetric Ring-Opening Aminolysis of 4,4-Dimethyl-3,5,8-trioxabicyclo[5.1.0]octane Catalyzed by Titanium/BINOLate/Water System: Evidence for the Ti(BINOLate)₂-Bearing Active Catalyst Entities and the Role of Water

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Abstract: The mechanism of the enantioselective ring-opening aminolysis of 4,4-dimethyl-3,5,8-trioxabicyclo[5.1.0]octane with benzylamine, catalyzed by the titanium-BINOLate species generated in situ from a mixture of enantiopure BINOL (1,1'-bi-2-naphthol), Ti(OⁱPr)₄, and H₂O in the presence of benzylamine in toluene, was investigated in detail using a combination of reaction profile measurements, nonlinear effect (NLE) studies, solution ¹H NMR analysis, electrospray ionization mass spectrometry (ESI-MS), as well as the results obtained from screening of dynamic catalyst library of complexes L_a/Ti/L_b (L_a or L_b = chiral diol ligands). The BINOL-to-titanium ratio and the presence or absence of water in the catalytic system were found to exert profound influences on both reactivity and enantioselectivity of the reaction. The NLE studies revealed that the titanium species involved in the catalysis should contain more than one BINOL unit, either within or at the periphery of the catalytic cycle. ESI-MS analysis of the catalytic systems provided strong support in favor of the mechanistic proposal that titanium complexes bearing the Ti(BINOLate)₂ moiety should be the active species responsible for the catalysis, which was further confirmed by the observation of synergistic effect of the heteroligand combinations during screening of the dynamic catalyst library. ESI-MS analysis of the reaction system indicated that water does not take part in the catalyst generation, which is an unprecedented finding in contrast to the previous mechanistic understandings in the titanium catalytic chemistry involving the participation of water. Most probably, water functions as a proton shuttle in the catalysis, facilitating the proton transfer between the reactants. Furthermore, the origin of (+)-NLE observed in the present catalytic system is rationalized on the basis of the ESI-MS analysis of the catalyst system prepared from a 1:1 *pseudoracemic* mixture of (*S*)-BINOL and (*R*)-3,3',6,6'-D₄-BINOL. Finally, the reactivity differences between several couples of epoxide/amine combinations were tentatively rationalized on the basis of the arguments on their relative coordination preferences, and several other aliphatic amines were also found to efficiently ring-open the titled epoxide in excellent enantioselectivities. The results from this study are expected to shed some light on the often elusive chemistry of Ti(IV)-based catalytic systems where water or molecular sieves (or alcohols, etc.) are found to play an important yet inexplicable role and may help the search for effective asymmetric Ti(IV) catalysts for other types of reactions.

Introduction

In the context of asymmetric catalysis, titanium complexes of BINOL and its derivatives are one of the most versatile

classes of chiral catalysts and have been used in a wide variety of highly enantioselective reactions.^{1–3} Despite this fact, how-

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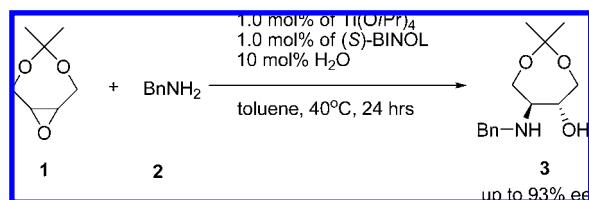
ever, the mechanistic elucidation of the multifarious aspects of the BINOL/Ti catalysis still remains an extremely challenging task for most reactions, and only some progress has been made in recent years.^{2,4} The catalytic species generated in situ from various titanium precursors and BINOL derivatives often display a rich structural chemistry and complicated behaviors in solution,^{2,5} as a result of the well-known flexibility of 1,1'-binaphthyl core,⁶ the variable coordination geometries of titanium, as well as its strong tendency to oligomerize into complicated supramolecular assemblies.^{5,7} Furthermore, variations in reaction parameters such as the stoichiometric ratio of chiral ligand-to-metal,^{8,9} the presence or absence of water^{5f,7f,10} and molecular sieves,¹¹ solvent, temperature, and so forth^{11e,12} have also been found to exert a profound influence on the catalytic behavior of the BINOL/Ti systems as a result of distinct catalyst structures involved in the reactions. Indeed, these can be regarded as common features for asymmetric Ti(IV) catalysis mediated with various chiral diols, whereby a slight modification on the catalyst composition can result in dramatically different

catalyst structures and catalytic behaviors.¹³ A classical example of the latter can be found in the pioneering studies by Kagan et al.¹⁴ and Modena et al.¹⁵ in the development of titanium alkoxide/tartrate catalysts for enantioselective thioether oxidation. Although using the standard Sharpless reagent for epoxidation of allylic alcohols (1:1 titanium alkoxide/tartrate derivative) in the sulfide oxidation reaction only gave racemic sulfoxides, variations made on the ligand-to-Ti ratios and/or the addition of water resulted in dramatic improvements in the enantioselectivity. In general, the titanium complexes of the chiral diols used in various asymmetric catalyses are generated in situ, which often results in the formation of a dynamic mixture of metal-containing species equilibrating with each other in solution. While this situation may be beneficial for facile fine-tuning of the catalysis through modifications on a diverse range of structural and reaction parameters, it often makes the unequivocal identification of the nature of active catalyst an extremely difficult and somewhat elusive goal.

Optically active *anti*- or *syn*-2-aminobutane-1,3,4-triol (ABT) equivalents, a class of highly functionalized compounds in various protected or unprotected forms, are extremely versatile chiral C4 building blocks for the efficient synthesis of a diversity of biologically active compounds, such as phytosphingosine,¹⁶ statine,¹⁷ and nelfinavir.¹⁸ Accordingly, several useful strategies for the synthesis of enantiopure ABT equivalents have been developed in recent years, either through the functional group manipulation of naturally occurring chiral compounds¹⁹ or via asymmetric syntheses where new stereogenic centers are stereoselectively formed in the products.^{18a} For practical utilization of ABT derivatives as versatile chiral synthons, the compounds should be available on large scales, with desired relative and absolute stereochemical structures, as well as in suitably protected forms for the selective transformation of their three hydroxyl groups and amino group. Unfortunately, many ABT synthetic routes²⁰ developed thus far cannot satisfy these requirements. Among the few exceptions, the Ti(IV)/BINOL-catalyzed asymmetric aminolysis of the meso epoxide 3,5,8-

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Scheme 1. BINOL/Ti(OiPr)₄-Catalyzed Asymmetric Aminolysis of the Epoxide **1** with Benzylamine



trioxabicyclo[5.1.0]octane (**1**) using benzylamine and its derivatives, developed by Inaba et al., can be regarded as one of the most efficient routes to optically pure ABT derivatives (Scheme 1).^{18,21} In this procedure, the reactions were performed in toluene (or 9:1 heptane/toluene) at 40 °C in the presence of the catalyst generated from (S)-BINOL and Ti(OiPr)₄ and water in a ratio of 1:1:10–20, affording the products in excellent stereoselectivity (>97% ee with 1-phenylethanamine as nucleophile 93% ee with benzylamine, respectively) with high conversions. The protected enantiopure 2-aminobutane-1,3,4-triols **3** and their enantiomers are accessible in bulk quantities using this protocol and have been successfully used as chiral intermediates in the practical syntheses of sphingamines¹⁶ and Nelfinavir (a potent HIV-protease inhibitor).^{18,20,21} Although a simplified molecular model of the catalytic species chelated by the epoxide **1** has been proposed by Inaba et al. on the basis of force field calculation of the model complex **1**-Ti(OMe)₄, no detailed mechanistic information was reported in the original procedure. The remarkable practical importance of the reaction coupled with the intriguing role of water in this and some other Ti-diol-catalyzed reactions prompted us to undertake a further study on the reaction mechanism as a part of our ongoing interests in developing titanium catalytic chemistry.²² Herein, we report the mechanistic investigation of the titled reaction using a combination of reaction profile measurements, nonlinear effect (NLE) studies, solution ¹H NMR analysis, electrospray ionization mass spectrometry (ESI-MS), as well as the screening of dynamic catalyst library of complexes L_a/Ti/L_b (L_a or L_b = chiral diol ligands).

Results and Discussion

Reaction Profiles: Influence of the Ratios of BINOL/Ti on Reactivity and Enantioselectivity. The work started with the examination on the potential impact of the BINOL/Ti molar ratios on the reactivity and enantioselectivity of the aminolysis of **1** with benzylamine. The reactions were performed in toluene (2.0 M of the epoxide and an equimolar amount of benzylamine) at 40 °C in the presence of 15 mol % water, with 1 mol % of Ti(OiPr)₄ loading under several different BINOL/Ti molar ratios. The reaction time courses were monitored by ¹H NMR analysis of aliquots taken from reaction mixtures at specified time periods, and ee values were assessed by HPLC determination

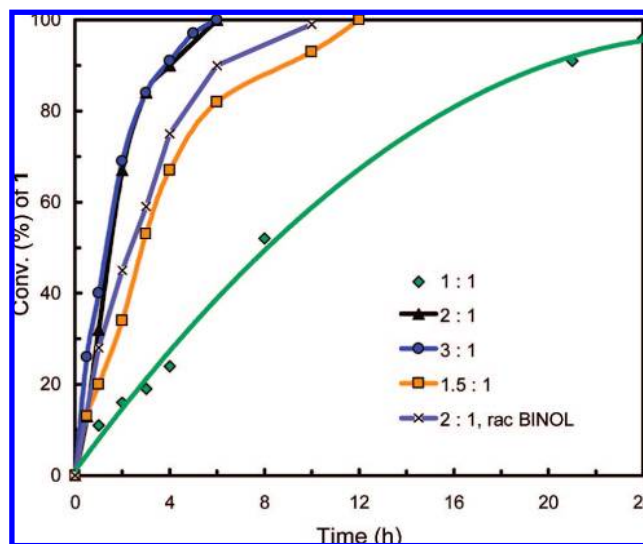


Figure 1. Reaction profiles of the (R)-BINOL/Ti(OiPr)₄/H₂O-catalyzed aminolysis of **1** with benzylamine using different (R)-BINOL/Ti molar ratios at 1 mol % loading of Ti(OiPr)₄ or racemic BINOL/Ti(OiPr)₄/H₂O-catalyzed aminolysis of **1**.

of the derivatized product using a chiral AD column (Figure 1). Control experiments showed that in the absence of BINOL the reaction was negligible after 24 h, and with a BINOL/Ti molar ratio of 0.5 only 11% conversion of **1** was observed within the same period. As shown in Figure 1, using a BINOL/Ti molar ratio of 1:1 (corresponding to Inaba et al.'s standard aminolysis conditions),²¹ the reaction took 24 h to reach a conversion of 96%. Further increase of the BINOL/Ti molar ratios up to 2:1 resulted in a considerable enhancement in the initial rate for the reaction, which took only 6 h to reach full conversion of **1** and did not show any incubation period in contrast to the 1:1 case. Moreover, the enantioselectivity of the reaction was also improved when the BINOL/Ti molar ratio was switched from 1:1 to 2:1 (92 vs 96% ee). Notably, further increment of the BINOL/Ti molar ratio to 3:1 only led to an almost identical reaction profile as the 2:1 system with a slight deterioration in enantioselectivity (92% ee). A plausible explanation of this behavior is the existence of some dynamic equilibria involving the active species, whose concentration can be affected by the subtle variation on the ligand-to-metal ratios in the present system.^{2,5a-d,7g} Therefore, under the present conditions, the BINOL/Ti molar ratio of 2:1 turns out to be optimal for the reaction in terms of both catalytic activity and enantioselectivity.

Impact of Water on Catalysis. We next proceeded to investigate the catalytic behavior of the aminolysis in the presence of various amounts of water. Water has often been shown to play an important yet somewhat intriguing role in chiral diol/Ti catalysis, usually by facilitating the formation of oxo- and/or hydroxo-bridged aggregates/oligomers through partial hydrolysis of the titanium alkoxide complexes.^{5,7,10g,23} For the aminolysis of **1** with benzylamine, the reactions were carried out by variation of the molar percentage of water in the system under the otherwise optimized conditions as above (BINOL/Ti ratio = 2:1), and the results were depicted in Figure 2. From the figure, it is clear that, although the reaction can still proceed without the addition of water, the presence of a certain amount of water (5–25 mol % relative to that of **1**) in

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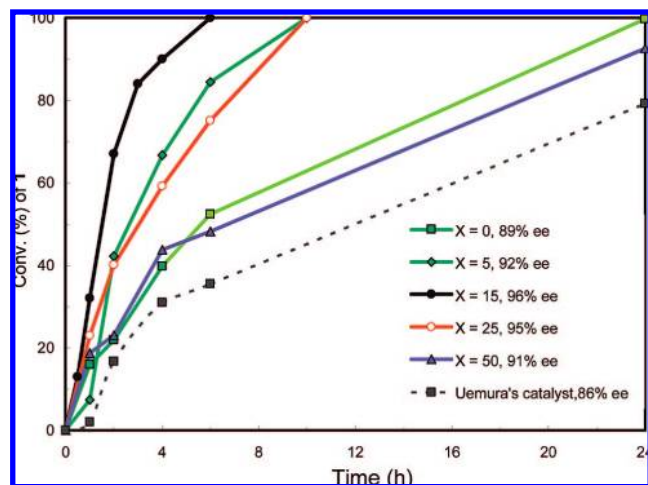


Figure 2. Influence of water content (X : mol % relative to **1**) on the BINOL/Ti(OiPr)₄/H₂O (molar ratio 1:2: X) catalyzed aminolysis of **1** with benzylamine at 1 mol % loading of Ti(OiPr)₄.

the system demonstrated a beneficial effect on both reactivity and enantioselectivity of the reaction ($X = 5, 15$, or 25 vs $X = 0$). Further increasing the water loading to 50 mol %, however, led to a significant deterioration in both reactivity and enantioselectivity, suggesting a partial decomposition of the catalyst might have occurred in the presence of too much water. Herein, 15 mol % of water (relative to the epoxide) is again found to be the optimal value. It is noteworthy that the catalyst composition of the present system is quite similar to that reported previously by Uemura et al. for asymmetric sulfoxidation,^{10e,f} both containing the (*R*)-BINOL/Ti(OiPr)₄/H₂O in a ratio of 2:1:15 (or 20). Since the solution structure of the catalyst (or precatalyst) of Uemura et al.'s catalyst system has been unequivocally elucidated by Salvadori et al. to be a tetrameric titanium species (BINOLate)₆Ti₄(μ₃-OH)₄,^{5h} we wondered whether it would be the same species that is working in the present reaction. For this purpose, we prepared the titanium catalyst following an analogous Uemura et al.'s procedure^{5h,10e,f} (i.e., adding 15 equiv of H₂O (relative to Ti) to the mixture of BINOL/Ti(OiPr)₄ (2:1) in toluene followed by BnNH₂), and the result is also depicted in Figure 2. It should be noted that here water is added before the addition of benzylamine nucleophile. Obviously, compared with the present reaction protocol, significant degradation in both reactivity and ee was observed by using Uemura et al.'s catalyst. Moreover, in this case only 2% conversion of **1** was obtained after 1 h reaction, indicating an incubation period is required for active catalyst formation. This behavior indicated that different catalytic species should be operating in the two reaction systems, and the tetrameric titanium species observed in Uemura et al.'s system should not be directly involved in the catalytic cycle of the current aminolysis reaction.

NLE Study. Given the pronounced effects of BINOL/Ti ratios and water on the activity/enantioselectivity observed in the aminolysis reaction, we proceeded to investigate the potential aggregation behavior of the titanium species through an NLE study. NLE has been established as an ubiquitous phenomenon in enantioselective catalysis and can usually be ascribed to the presence of diastereomeric homochiral or heterochiral catalytic species which are generated from the self-assembly of the metal ions with more than one chiral ligand of the same or opposite

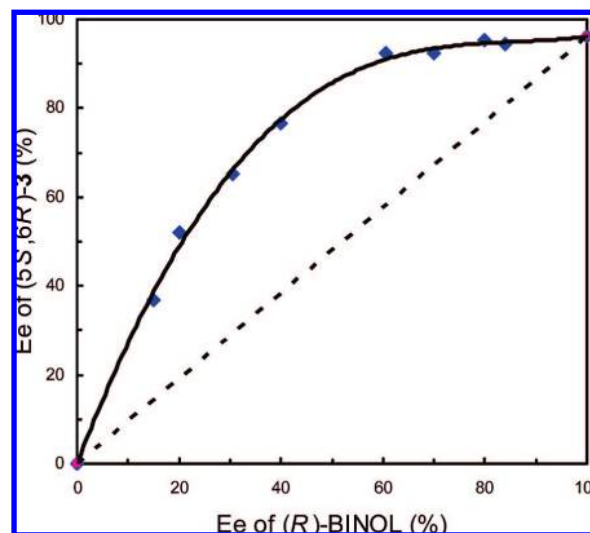


Figure 3. Positive NLE observed in the BINOL/Ti/H₂O-catalyzed enantioselective ring-opening aminolysis of epoxide **1** by benzylamine.

configurations.²⁴ Therefore, the study of NLE with nonenantiomerically pure catalysts has often been used as a powerful diagnostic tool for probing the nature and especially the aggregation behavior of the species involved in asymmetric catalysis. The presence of NLE has been observed in many BINOL/Ti-catalyzed enantioselective reactions (e.g., the glyoxylate-ene reactions,²⁵ the allylation²⁶ and aldol condensation of aldehydes,²⁷ sulfoxidations,^{10e,f} and Diels–Alder reactions^{11d}). Although the exact reason for observation of NLE in these BINOL/Ti catalytic systems varies from case to case, the simultaneous presence of various oxo- or hydroxo-bridged diastereomeric dimeric or oligomeric BINOL/Ti species with different thermodynamic stabilities and kinetic reactivities, formed by partial hydrolysis or under the influence of molecular sieves, has been proposed to be responsible for the origin of NLE.^{11,28}

Following the general procedure outlined in the previous section, the NLE of the present reaction was examined with BINOL of varying ee's under the otherwise identical conditions as above. As can be seen by the convex line plot of the data in Figure 3, positive NLE was observed for this catalytic system, which obviously indicates that diastereomeric complexes are formed either in the catalytic cycle or at its periphery. In other

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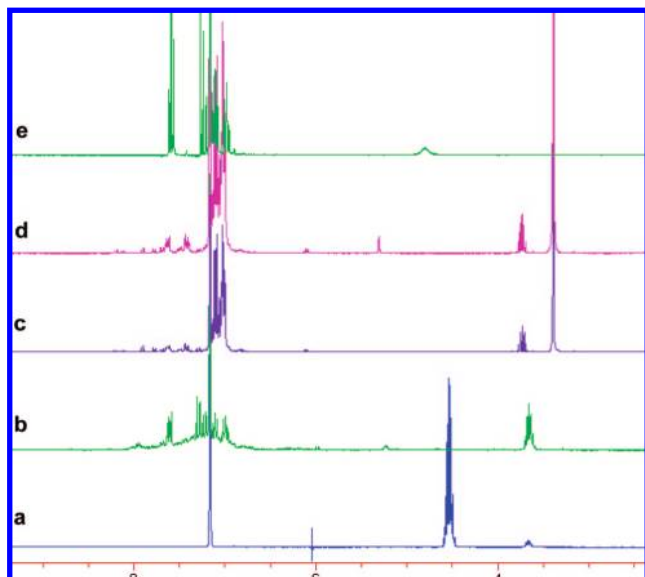


Figure 4. ^1H NMR spectra taken in C_6D_6 . (a) $\text{Ti}(\text{O}i\text{Pr})_4$, (b) $[(R)\text{-BINOL}/\text{Ti}(\text{O}i\text{Pr})_4]$ (2:1), (c) $[(R)\text{-BINOL}/\text{Ti}(\text{O}i\text{Pr})_4/\text{BnNH}_2]$ (2:1:10), (d) $[(R)\text{-BINOL}/\text{Ti}(\text{O}i\text{Pr})_4/\text{BnNH}_2/\text{H}_2\text{O}]$ (2:1:10:15), and (e) $(R)\text{-BINOL}$.

words, the pronounced (+)-NLE usually suggests the involvement of two or more BINOL ligands in the formation of active or inactive titanium species, and, if interpreted using Kagan's ML_2 model (vide infra),^{24a,29} the heterochiral BINOL/Ti complexes should be less reactive than any of the homochiral ones. Indeed, when the *rac*-BINOL/ $\text{Ti}(\text{O}i\text{Pr})_4$ (2:1) system was used, the reaction rate was lower than that of the enantiopure (R) -BINOL/ $\text{Ti}(\text{O}i\text{Pr})_4$ (2:1) system under otherwise identical conditions (Figure 1).

To probe the possibility of the involvement of enantioenriched amino alcohol product in the active species, the variation of the enantioselectivity with time was determined by using isopropylamine instead of benzylamine as the nucleophile in the aminolytic reaction of **1**, since in the former case the product ee could be easily determined by chiral GC without the need of further derivatization. The experiment was performed under identical conditions as above using enantiopure BINOL, and the ee's of the product were monitored during the reaction course by removing aliquots at varying time durations. The reaction was completed at 8 h, and the ee's were found to be constant over the whole reaction course. The absence of ee variations during the reaction makes it unlikely that the amino alcoholic product is involved in the catalytically active species. Instead, the enantiopure BINOL ligand must be the sole cause responsible for the efficient enantiocontrol of the reaction.

^1H NMR Characterization of Catalyst System. Until now little was known about the nature of the catalytic entity responsible for the enantioselective reaction. The room-temperature ^1H NMR spectra of the catalytic system (Figure 4) before the addition of the epoxide was taken to provide a preliminary assessment of the nature of the various titanium species equilibrating in solution (under the reaction conditions) before the reaction. As shown in Figure 4, upon mixing 2:1 (R) -BINOL/ $\text{Ti}(\text{O}i\text{Pr})_4$ in C_6D_6 , we saw that the ^1H NMR spectrum of the mixture shows broad bulgelike resonances at the aromatic region (spectrum b), indicating the presence of a mixture of slowly

equilibrating aggregates or oligomeric species. The isopropoxide methine proton signal at δ 4.53 of $\text{Ti}(\text{O}i\text{Pr})_4$ (spectrum a) was shifted upfield to 3.65 (spectrum b), suggesting the complete protonation of isopropoxide by BINOL and its release from the Ti binding to become the free isopropyl alcohol.³⁰ With the addition of 10 equiv of benzylamine [relative to $\text{Ti}(\text{O}i\text{Pr})_4$] and aging the system for 30 min, however, the complex proton signals at the aromatic region became much more well-resolved with significant simplification of the spectrum (spectrum c), indicating that addition of benzylamine promotes a convergence of a manifold of species into a limited number of species (this is in accord with the ESI-MS data that only a limited number of species evolved from a complex spectrum upon addition of BnNH_2 , vide infra). Visual inspection of the solution in the NMR tube showed that the dark red BINOL/Ti solution turned yellow immediately upon addition of benzylamine, suggesting the coordination of the benzylamine to titanium occurred in the system. Further addition of 15 equiv of water [relative to $\text{Ti}(\text{O}i\text{Pr})_4$] to the system did not result in much alteration in the appearance of the spectrum (spectrum d), suggesting that there were no appreciable changes in the solution structures of the Ti/BINOL species, implying water is not necessary for the formation of the active catalyst at least up to this stage, as it did not cause any obvious structural reorganization of the catalyst by actions such as hydrolysis.

ESI-MS Analysis of the Catalytic System before Addition of the Epoxide. To further probe the nature of the various titanium species equilibrating in solution under the reaction conditions and to get information on their evolution to the active species, ESI-MS was employed as an analytical tool to assess the reaction system before and after the addition of the epoxide. ESI-MS has been applied as a powerful tool to characterize inorganic and organometallic species in solution, and plenty of precedents can be found in the literature where ESI-MS has been applied to the identification of different polynuclear metal complexes in rapid exchanging systems.³¹ Furthermore, ESI-MS has also been successfully used to understand the unique nature of the catalytic species in a variety of reactions.³² For ESI-MS characterization of the present catalytic system before the addition of the epoxide, the spectra were collected in

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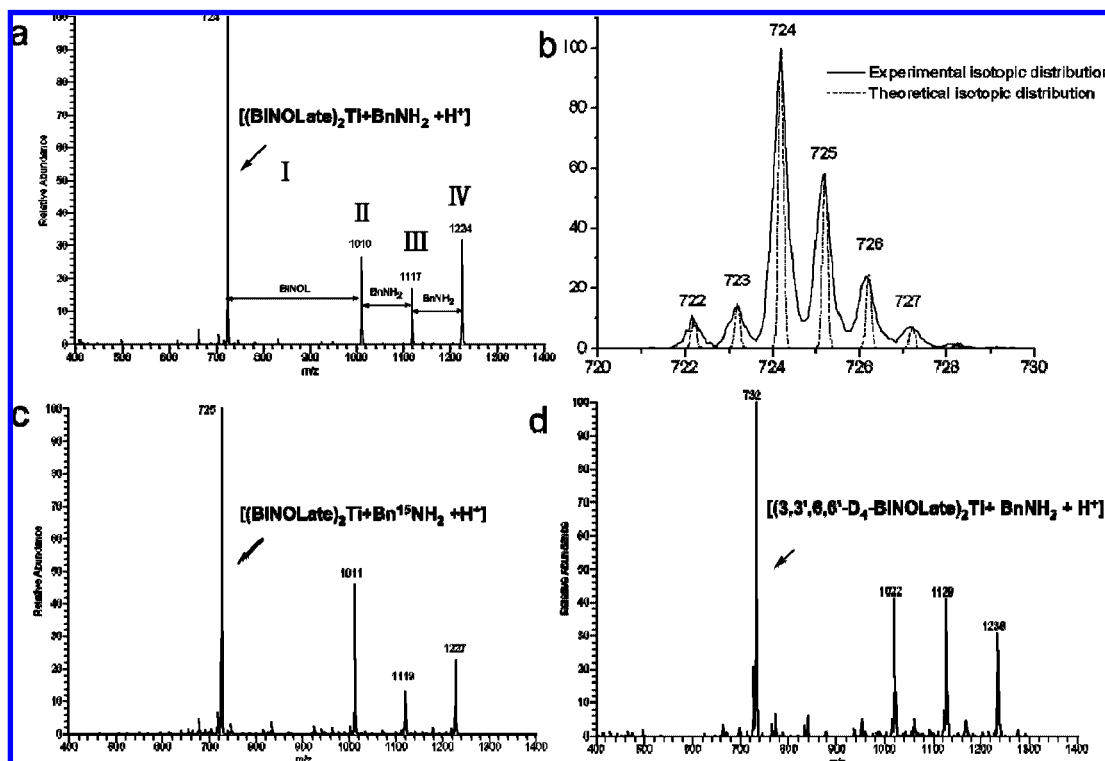


Figure 5. ESI-MS spectra of the catalyst systems before the addition of the epoxide: (a) (*R*)-BINOL/Ti(OiPr)₄/BnNH₂ (2:1:10), (b) experimental isotopic distribution and theoretical simulation of the peak at *m/z* = 724, (c) (*R*)-BINOL/Ti(OiPr)₄/Bn¹⁵NH₂ (2:1:10), and (d) (*R*)-3,3',6,6'-D₄-BINOL/Ti(OiPr)₄/BnNH₂ (2:1:10).

positive-ion mode by stepwise diluting the toluene solutions of (*R*)-BINOL/Ti(OiPr)₄ (2:1), (*R*)-BINOL/Ti(OiPr)₄/BnNH₂ (2:1:10), or (*R*)-BINOL/Ti(OiPr)₄/BnNH₂/H₂O (2:1:10:15), respectively, in acetonitrile. Tandem mass spectrometry (MS/MS) analysis provided useful information on the relative metal–ligand bond strengths. The simulation of the observed isotopic distributions of the characteristic well-resolved peaks and the use of isotope-labeled benzylamine or BINOL gave an unambiguous identification of all the Ti-containing ions in the system. A combined application of these ESI-MS techniques provided clear insight into the structural elucidation of the Ti(IV) complexes under study. First, the positive ion spectrum collected for the 2:1 mixture of (*R*)-BINOL/Ti(OiPr)₄ showed a complex pattern with a multitude of poorly resolved peaks (Figure S1 in Supporting Information (SI)), indicating the presence of many titanium species which is in keeping with the NMR result and the well-known complexity of BINOL/Ti(OiPr)₄ mixtures.^{4–12} Then, adding 10 equiv [relative to that of Ti(OiPr)₄] of benzylamine to the toluene solution of (*R*)-BINOL/Ti(OiPr)₄ (2:1) and aging the system for 30 min resulted in a dramatic evolution of the ESI-MS spectrum: as shown in Figure 5a, only four intense peaks at *m/z* = 724 (C₄₇H₃₄NO₄Ti⁺), 1010 (C₆₇H₄₈NO₆Ti⁺), 1117 (C₇₄H₅₇N₂O₆Ti⁺), and 1224 (C₈₁H₆₆N₃O₆Ti⁺), compositionally corresponding to [(BINOLate)₂Ti + BnNH₂ + H]⁺ (I), [(BINOLate)₂Ti + BnNH₂ + BINOL + H]⁺ (II), [(BINOLate)₂Ti + 2BnNH₂ + BINOL + H]⁺ (III), and [(BINOLate)₂Ti + 3BnNH₂ + BINOL + H]⁺ (IV), respectively, predominate in the clean spectrum. This is in agreement with the corresponding NMR result discussed above. Isotopic pattern simulation of the base peak at *m/z* = 724 agreed well with the observed isotopic distribution (Figure 5b), thus unambiguously establishing the elemental composition of the observed ions. Further evidence of the number of benzylamine and BINOL molecules

present in each of these ions came from the ESI-MS of a similar system using ¹⁵N-labeled benzylamine or 3,3',6,6'-teradeuterium-labeled (*R*)-1,1'-bi-2-naphthol ((*R*)-3,3',6,6'-D₄-BINOL) in catalyst preparation, respectively (Figure 5c,d). It is interesting to note that all four detected species contain only one Ti atom in their formula, despite the well-known tendency of aggregation for titanium complexes. Remarkably, further addition of 15 equiv of water to the above system [(*R*)-BINOL/Ti(OiPr)₄/BnNH₂ = 2:1:10] did not result in any significant changes in the ESI-MS spectrum (Figure S2a in SI), suggesting that water does not play any role in new species (or precatalyst) formation despite the significant amount of water relative to Ti. This is somewhat surprising in that most of the Ti/alkoxide systems reported thus far demonstrate a facile tendency to hydrolysis, forming oxo-, hydroxo-, or water-containing (or bridged) multinuclear (or dinuclear) Ti species (aggregates) in the presence of water.

Tandem MS spectroscopic analysis of ions I–IV was performed to ascertain the relative metal–ligand bond strengths and to confirm the assignment of their identities outlined above (Figure 6). MS/MS analysis shows that the base peak ion I fragments by losing one benzylamine molecule (724 – 617 = 107 Da); such a fragmentation pattern is strong evidence for the coordination of a benzylamine to the titanium center surrounded by two BINOLates (Figure 6a). Similarly, the MS/MS spectrum of ion II (*m/z* = 1010) (Figure 6b) collected under identical experimental conditions only fragments to ion I, resulting from the loss of one molecule of BINOL (286 Da), indicating a distinct difference in bonding strengths exists among the three BINOL(ate) moieties and titanium in the ion. One BINOL molecule only interacts relatively weakly with the rest part of the complex. Remarkably, the MS/MS spectra of ions III (*m/z* = 1117) (Figure 6c) and IV (*m/z* = 1224) (Figure 6d) collected under the same experimental conditions produce only

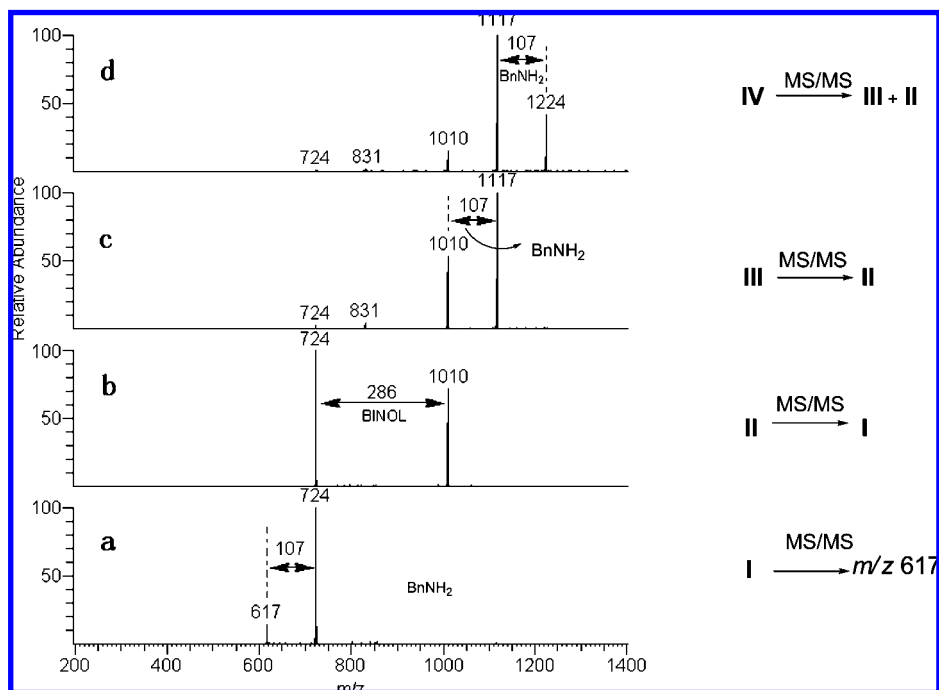


Figure 6. MS/MS spectra of the major ions I–IV observed in Figure 5.

fragments corresponding to ions with the loss of one or two molecule(s) of benzylamine. The persistent occurrence of the common structural feature $[(\text{BINOLate})_2\text{Ti}]$ strongly indicates that the presumably double-chelated core structure remained intact through the electrospray process, whereas the third relatively labile BINOL in weak peaks II, III, and IV should be linked to the core through weak interactions such as H-bonding.³³ It is worth noting here that although a Ti complex with the composition $[(\text{BINOL})\text{Ti}(\text{BINOLate})(\text{OiPr})_2]$ somewhat similar to that of $[(\text{BINOLate})_2\text{Ti}]$ was proposed by Mikami and Matsukawa in 1997 on the basis of ^{13}C NMR determination,³⁴ the MS data discussed above is the first unequivocal evidence of the species.

Furthermore, ESI-MS spectrum of Inaba et al.'s catalyst system for the same reaction $[(R)\text{-BINOL}/\text{Ti}(\text{OiPr})_4/\text{BnNH}_2/\text{H}_2\text{O}$ (1:1:10:15)] (Figure S2b in SI) is very similar to that in Figure 5a without the appearance of new peaks, suggesting that the same mechanism is operating in both systems $[(R)\text{-BINOL}/\text{Ti}(\text{OiPr})_4 = 2:1$ or $1:1]$, and the rate difference observed in Figure 1 for the two systems can be attributed to the difference in the concentration rather than the identity of the involved active species. Remarkably, this might also provide an alternative interpretation for the observed distinction in catalytic performance in similar 2:1 and 1:1 diol/Ti systems.

ESI-MS Analysis of the Catalytic System after the Addition of the Epoxide. Subsequently, ESI-MS determinations were performed on the reaction system after addition of the epoxide $[(R)\text{-BINOL}/\text{Ti}(\text{OiPr})_4/\text{BnNH}_2/\text{H}_2\text{O}/\text{epoxide} = 2:1:10:15:10]$. The spectra were collected under identical ESI-MS experimental conditions as above, and the sample was taken immediately after addition of the epoxide (1 min) to get the information of the system before completion of the reaction. As shown in Figure 7, a quite clean and simple-looking spectrum demonstrates the appearance of a number of new species. Data analysis and peak

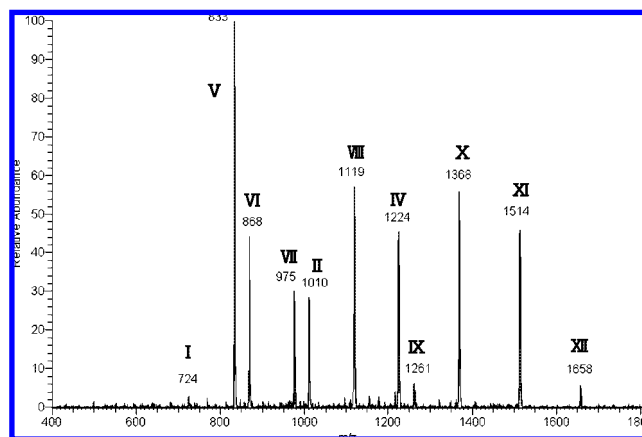


Figure 7. ESI-MS spectrum of the $[\text{BINOL}/\text{Ti}(\text{OiPr})_4/\text{BnNH}_2/\text{H}_2\text{O}/\text{epoxide} = 2:1:10:15:10]$ system.

assignment using procedures similar to the last section (for details, see SI) revealed that all the significant peaks contain a mononuclear Ti species with different number of BINOL(ate) units, and all the species except the one at $m/z = 833$ can be assigned to bear a $\text{Ti}(\text{BINOLate})_2$ core together with the weak association of varying numbers of BINOL (0 or 1), benzylamine (0 to 3), epoxide (0 to 5), and/or the amino alcohol product (0 to 3) molecules. Again, no water- or hydroxo- or oxo-containing species was observed, confirming the innocent (or spectator) nature of the water on the catalyst structure formation. The Ti species coordinated with epoxide alone is not detected in the reaction mixture, which seems to imply its high reactivity. The base peak at $m/z = 833$ ($\text{C}_{48}\text{H}_{53}\text{N}_2\text{O}_8\text{Ti}^+$) compositionally corresponds to the $[(\text{BINOLate})\text{Ti}]^{2+}$ unit coordinated with one or two deprotonated amino alkoxide products ($\mathbf{3}\text{-H}^+$), that is, $[(\text{BINOLate})\text{Ti}(\text{BnNH}_2)(\text{epoxide})(\mathbf{3}\text{-H}^+)]^+$ or $[(\text{BINOLate})\text{Ti} + 2(\mathbf{3}\text{-H}^+) + \text{H}^+]^+$. MS/MS analysis of this ion (Figure S4 in SI) demonstrates no fragments corresponding to the loss of either benzylamine or the epoxide, suggesting that the latter should

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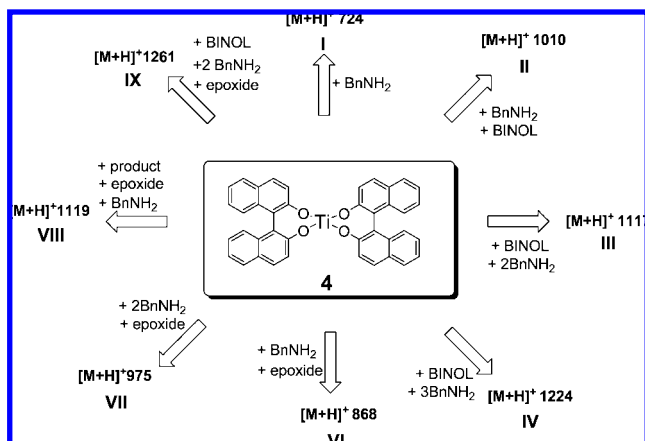


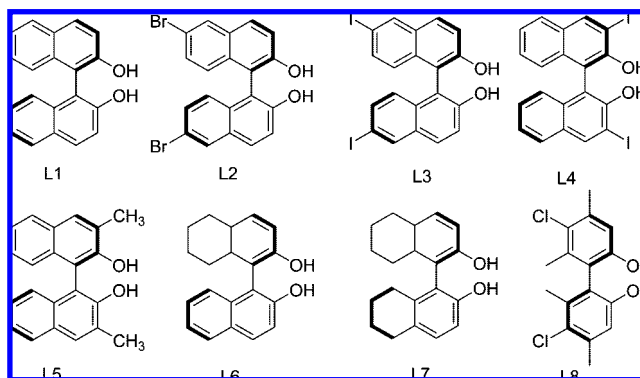
Figure 8. Common structural motif **4** in the Ti species observed in the ESI-MS spectra of the reaction system before or after the addition of epoxide **1**.

be the plausible species corresponding to the peak at $m/z = 833$. This is unlikely a catalytically active species for the following reasons. First, if Ti is chelated with two amino alcohol molecules and one BINOLate, then without ligand dissociation the complex $[\text{BINOLate}/\text{Ti}/(\mathbf{3})_2]$ would be coordinatively saturated and no longer accessible for epoxide activation. Second, dissociation of an amino alcohol **3** from this species would produce a Ti complex (BINOLate/Ti/**3**) bearing one molecule of BINOLate and one chiral amino alcohol **3**, respectively. Since the latter is also highly enantioenriched, it is thus expected to exhibit some perturbation on ee values during the reaction course, which is in contradiction with the observation mentioned above (vide supra). The considerable decrease in the relative peak intensity at $m/z = 724$ after the addition of epoxide **1** (compared with the base peak **I** in Figure 5) suggests that the complex $[(\text{BINOLate})_2\text{Ti}(\text{BnNH}_2)]$ might be the catalyst precursor whose concentration level should decrease significantly during the reaction course by consumption with the stronger coordinating epoxide **1** and/or the amino alcohol product **3**.

To summarize this section, the potential presence of any polynuclear titanium species is not detected in the positive ion ESI-MS of the systems either before or after the addition of the epoxide, which provides the strong support that water does not take part in the catalyst formation. Moreover, a mononuclear Ti coordinated by two BINOLates, $\text{Ti}(\text{BINOLate})_2$ (**4**), is found to represent the dominant structural feature which is present in almost all the detected species (Figure 8) and thus might be persistent throughout the whole catalysis.

Screening of Dynamic Catalyst Library of Complexes $L_a/\text{Ti}/L_b$. Although the ESI-MS analysis and the NLE study is strongly indicative of the involvement of $\text{Ti}(\text{BINOLate})_2$ -containing species in the catalysis, it is still not clear whether it is acting as the protagonist within or simply as a catalyst precursor at the periphery of the catalytic cycle. Here, the observation of synergistic effect in the present Ti(IV)-catalyzed reaction through the combinatorial use of binary mixtures of chiral diol ligands provided the ultimate proof in favor of the direct involvement of $\text{Ti}(\text{BINOLate})_2$ -containing species in the catalytic cycle. The concept of asymmetric activation was

Chart 1. Collection of Chiral Diol Ligands



proposed by Mikami et al.^{34,35} and has been successfully applied in a variety of catalytic asymmetric reactions.^{35–37} The asymmetric activation can in principle take effect whenever the enantioselectivity-determining transition state for a catalytic asymmetric reaction contains the metal M simultaneously coordinated with two ligands L_a and L_b (same as or different from each other). Upon mixing of two such ligands L_a and L_b with metal M, two homocombinations ML_aL_a and ML_bL_b as well as the heterocombination ML_aL_b can be obtained which are in equilibrium with each other in the catalyst solution. When ML_aL_b is more active and more selective than either of the complexes ML_aL_a or ML_bL_b , the mixture of all three catalysts may well lead to an enhanced enantioselectivity than either of the catalyst ML_aL_a or ML_bL_b used alone.³⁶ On the one hand, asymmetric activation can be used as a powerful strategy for catalyst optimization; on the other hand, it should also provide unequivocal evidence that two or more ligands are directly involved in the enantioselectivity-determining transition state and thus may well serve our purpose. From this point of view, we further screened a library of Ti/diol complexes with various $L_a/\text{Ti}(\text{OiPr})_4/L_b$ (molar ratio 1:1:1) combinations in the present reaction under otherwise identical conditions as above, through the use of a collection of enantiopure chiral diols depicted in Chart 1. As can be seen from the results in Table 1, the heterocombinations of L_4/L_7 indeed afforded a dramatically enhanced ee value (92%, entry 29) relative to either of the two homocombinations (both are 7%, entries 4 and 7). Remarkably, this improvement in ee can only be achieved in a catalytic cycle where the enantioselectivity-determining transition state simultaneously bears more than one chiral ligand in the active site. Furthermore, slight improvement in ee values can also be observed for $L_1/\text{Ti}/L_2$, $L_1/\text{Ti}/L_3$, $L_3/\text{Ti}/L_6$ combinations relative to their homocounterparts $L_1/\text{Ti}/L_1$, $L_2/\text{Ti}/L_2$, $L_3/\text{Ti}/L_3$, and $L_6/\text{Ti}/L_6$ (entries 9, 10, and 24 vs entries 1–3, 6). Similar

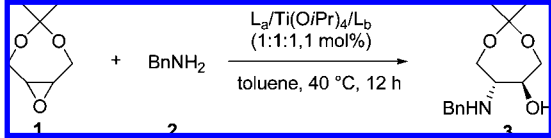
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Table 1. Screening of Various $L_a/Ti/L_b$ Catalyst Combinations (L_a and L_b = Chiral Diols in Chart 1) in the Ring-Opening Reaction of **1** with Benzylamine



entry	L_a/L_b	yield (%)	ee (%) ^a
1	L_1/L_1	96	96
2	L_2/L_2	94	95
3	L_3/L_3	94	96
4	L_4/L_4	26	7
5	L_5/L_5	0	
6	L_6/L_6	8	14
7	L_7/L_7	12	7
8	L_8/L_8	16	26
9	L_1/L_2	99	98
10	L_1/L_3	95	98
11	L_1/L_4	81	85
12	L_1/L_5	92	94
13	L_1/L_6	90	90
14	L_1/L_7	85	92
15	L_1/L_8	91	80
16	L_2/L_3	96	94
17	L_2/L_4	84	78
18	L_2/L_5	90	96
19	L_2/L_6	94	96
20	L_2/L_7	98	96
21	L_2/L_8	90	92
22	L_3/L_4	95	94
23	L_3/L_5	93	96
24	L_3/L_6	91	98
25	L_3/L_7	95	97
26	L_3/L_8	86	96
27	L_4/L_5	15	28
28	L_4/L_6	32	19
29	L_4/L_7	27	92 ^b
30	L_4/L_8	31	14 ^b
31	L_5/L_6	12	0
32	L_5/L_7	6	10
34	L_6/L_7	0	
35	L_6/L_8	47	21
36	L_7/L_8	0	

^a The absolute configuration of all the amino alcohol products was determined to be (5*S*, 6*R*) unless otherwise specified. ^b The absolute configuration of all the amino alcohol products was determined to be (5*R*, 6*S*).

enhancement in reactivity can also be found for the $L_6/Ti/L_8$ heterocombination as compared with their respective homocombinations (entry 35 vs 6 and 8). This is the ultimate proof that the Ti species bearing the $Ti(BINOLate)_2$ moiety is(are) the active catalyst(s) within the catalytic cycle, directly participating in the aminolytic ring-opening of the epoxide. This interpretation is also supported by the poor reactivity and enantioselectivity of the $L_4/Ti(OiPr)_4/L_4$ and $L_5/Ti(OiPr)_4/L_5$ systems (entries 4 and 5), since the use of 3,3'-disubstituted BINOLs is expected to be unfavorable for the formation of $Ti(BINOLate)_2$ moiety which is sterically demanding at the Ti center. Last but not least, ESI-MS of the catalyst system with the composition (*R*)-BINOL/ $Ti(OiPr)_4$ /*R*)-3,3',6,6'-*D*₄-BINOL provided unequivocal evidence for the presence of heteroligand complex along with the corresponding homocombinations in the mixture (vide infra, Figure 9a). It is therefore conceivable that, in related $L_a/Ti(OiPr)_4/L_b$ systems, the presence of similar heterocombination complexes (such as $L_4/Ti/L_7$) with an activity higher than those of their homocombination counterparts should

be the underlying structural reason for the observation of the synergistic effect of two-component ligands.

Proposed Mechanism for the Aminolysis of Epoxide 1 Catalyzed by the BINOL/ $Ti(OiPr)_4$ / H_2O System. On the basis of the afore-discussed reaction profile studies, ¹H NMR and ESI-MS analyses, and the beneficial synergistic effect of the binary ligands exhibited in dynamic catalyst library of complexes $L_a/Ti/L_b$, we propose a plausible mechanism for the enantioselective aminolysis of epoxide **1** by benzylamine using the BINOL/ $Ti(OiPr)_4$ / H_2O catalyst system. As outlined in Scheme 2, mixing of BINOL and $Ti(OiPr)_4$ in toluene results in the formation of a multitude of BINOL/Ti species complexes equilibrating with each other, which reorganized into a limited number of mononuclear Ti species (such as **5**) bearing the $Ti(BINOLate)_2$ moiety upon the addition of an excess amount of benzylamine. The mononuclear Ti species **5**, containing at least one coordinated benzylamine for which the exact structure is still not clear at the present stage, is proposed to be composed of the titanium coordinated with two chelating BINOLate in cis configuration. Further addition of a certain amount of water does not cause any significant structural variation of the observed Ti species. This apparently exotic behavior can be attributed to the coordination power of benzylamine, which can not only resolve the Ti/BINOL mixtures into well-defined structures, but also effectively suppress the competitive coordination of water to Ti and therefore prevent the otherwise hydrolysis. Furthermore, this ligating ability of benzylamine might also have some influences on the coordinating activation of the epoxide **1**. Since Inaba et al. demonstrated that the bichelating coordination of an epoxide seems to be necessary for the reaction to occur,²¹ it is likely that the coordinated benzylamine has to be replaced by the chelating epoxide **1** via ligand exchange to form complex **6** before sufficient activation of the epoxide can be achieved. It is notable here that, in the ESI-MS spectrum of the reacting system (Figure 7), the relative abundance of the peak at $m/z = 724$ (species **5** in Scheme 2) decreases sharply as compared with that in Figure 5a, consistent with **5** being further transformed into other species such as **6** during the reaction process. Intriguingly, the expected peak corresponding to the proposed active species **6** did not appear in Figure 7, presumably as a result of its high reactivity (thus low concentration). Now that Ti-activated epoxide species **6** is ready for the nucleophilic attack from the amine, then what is the function of water in the catalysis? From the ESI-MS analyses of the system before and after the reaction, it is unlikely that water acts as a Lewis base donor (OH^- , O^{2-} , or H_2O itself) to take part in the active catalyst formation even though coordination vacancy (vacant site) seems to be available on the $(BINOLate)_2Ti(BnNH_2)$ species. However, from the reaction profile study there is significant difference in both reactivity and enantioselectivity in the presence or absence of water; therefore, water must have taken a part in the rate- and enantioselectivity-determining transition state. Most probably, water can affect the reaction by acting as a proton shuttle to facilitate the catalytic turnover (i.e., as both proton acceptor and donor) to transfer protons between the amine group and forming (or formed) amino alkoxide group through hydrogen bonding with both. The backward attack of the amine on the epoxide carbon requires some species to assist the accompanying proton transfer. Although the amine in solution can also accomplish the proton transfer, it is less efficient than the smaller amphoteric water which can enter into the active site of the catalytic assembly. Although this type of behavior has also been proposed in some water-containing organometallic catalytic

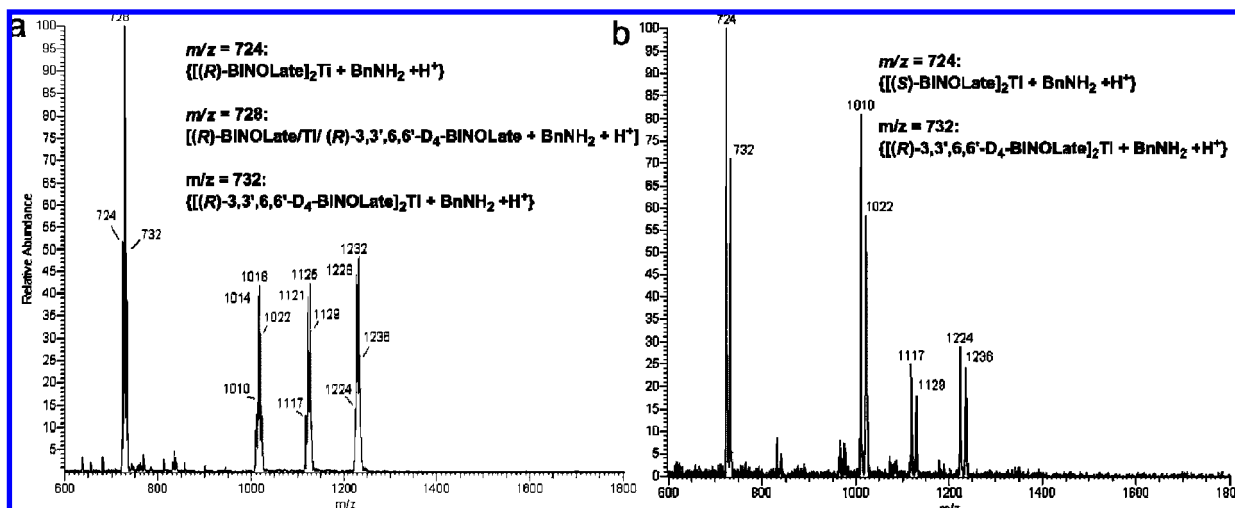
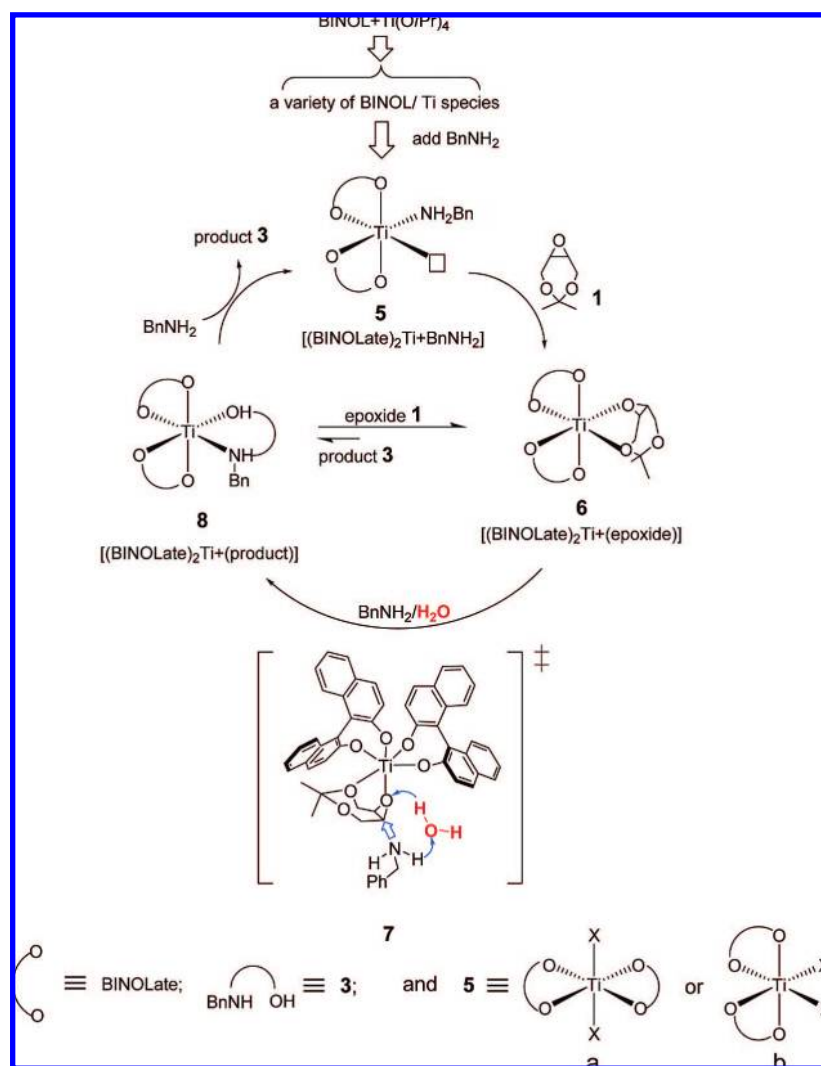


Figure 9. ESI spectra of (a) *(R)*-BINOL/Ti(OiPr)₄/*(R)*-3,3',6,6'-D₄-BINOL/BnNH₂ (1:1:1:10), and (b) *(S)*-BINOL/Ti(OiPr)₄/*(R)*-3,3',6,6'-D₄-BINOL/BnNH₂ (1:1:1:10).

Scheme 2. Proposed Mechanism for the Asymmetric Ring-Opening Aminolysis of Epoxide **1** Using BINOL/Ti/Water Catalyst System



systems,³⁸ it has never been demonstrated or reported for chiral diol/Ti systems presumably as a result of the well-known aggregation behavior of Ti complexes. This finding may also shed some light on the often elusive chemistry of Ti(IV)-based

catalytic systems where water or molecular sieves (often containing a certain amount of water) play an important yet inexplicable role^{8,11,39} and may help to further enrich the already extremely versatile titanium/diol chemistry. While the introduc-

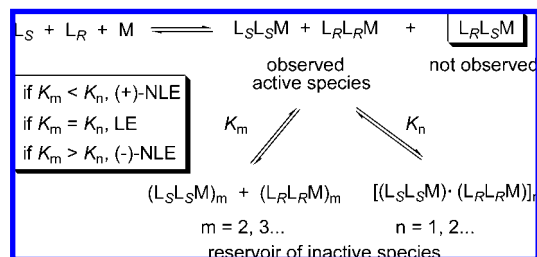
tion of a certain amount of water (5–15 mol%) is beneficial to the title reaction, the presence of excessive water will more or less destroy the delicate coordination equilibria and reduce the concentration of active species by the formation of inactive oxo-bridged Ti oligomers, leading to a lowering in reactivity. An optimal balance is reached somewhere in Figure 2, which is in agreement with the mechanistic interpretation.

A transition-state model **7** was tentatively proposed for the aminolysis step by taking into account these considerations. The Ti center in Ti(BINOLate)₂ is chelated with the epoxide **1**, which, via the assistance of water as the proton shuttle, undergoes the backward nucleophilic attack from benzylamine to form the amino alcohol product bound on the Ti(BINOLate)₂ moiety **8**. Subsequent dynamic ligand exchange of **8** with either benzylamine or the epoxide will release the amino alcohol product **3** with the regeneration of catalytic species **5** or **6**, which can resume the further catalytic cycle.

According to this proposed mechanism, it seems plausible that the NLE observed in the reaction can be rationalized using Kagan et al.'s ML₂ model.^{24,29} By this model, three different BINOL/Ti complexes, that is, two homochiral combinations (*R*)-BINOLate/Ti/(*R*)-BINOLate and (*S*)-BINOLate/Ti/(*S*)-BINOLate, and one heterochiral combination (*R*)-BINOLate/Ti/(*S*)-BINOLate (here we temporarily omit the presence of BnNH₂ in the discussion for the sake of clarity), can be generated in situ by mixing racemic or enantioenriched BINOL with Ti(O-*i*Pr)₄ in toluene, and it is tempting to assume that the pronounced (+)-NLE might be caused by the more stable and less reactive heterochiral complex. To probe the structural origin of the NLE, ESI-MS spectrum (Figure 9b) was collected on the catalyst system prepared from a 1:1 *pseudoracemic* mixture of (*S*)-BINOL and (*R*)-3,3',6,6'-D₄-BINOL under the otherwise identical conditions as above so as to minimize the stereoelectronic effect of ligand composition on the formation of the heterochiral complex. Surprisingly, while both of the homochiral combinations are clearly distinguishable in Figure 9b [e.g., the peaks at *m/z* = 724 for (*S*)-BINOLate/Ti/(*S*)-BINOLate and 732 for (*R*)-3,3',6,6'-D₄-BINOLate/Ti/(*R*)-3,3',6,6'-D₄-BINOLate], the expected peak at *m/z* = 728 for the heterochiral complex (*S*)-BINOLate/Ti/(*R*)-3,3',6,6'-D₄-BINOLate did not appear at all. The same is true for other groups of peaks in Figure 9b, which is in contradiction to the prediction by the ML₂ model. For comparison purpose, ESI-MS spectrum (Figure 9a) was also collected on a catalyst system with compositions identical to those in Figure 9b except that (*R*)-BINOL is used instead of (*S*)-BINOL. Remarkably, all three expected assemblies (i.e., L_a/Ti/L_a, L_b/Ti/L_b, and L_a/Ti/L_b) are detected in this case as shown in Figure 9a, indicating that the BINOL ligands with same absolute configurations should have a stronger tendency to form ML₂-type complexes in the present reaction system.

According to Blackmond's approach,^{24b} a kinetic analysis of the NLE can provide an independent confirmation of the models of NLE. Kinetic analysis of the NLE for the present system using the data of reaction rate vs ligand ee (Figure S12) revealed the racemic system has ca. 67% activity of the enantiopure system, considerably higher than the value deduced using Kagan

Scheme 3. Plausible Model of NLE in the Title Reaction System



et al.'s original ML₂ model (ca. 0.4). These results in combination with the absence of the heterochiral species ML_RL_S as shown in Figure 9b suggest that Kagan et al.'s original ML₂ model might not be applicable to the present system. Although the origin of NLE can be rationalized in many ways, the formation of some types of Ti species containing both (*R*)- and (*S*)-BINOL ligands should be essential. Thus, we propose a tentative explanation similar to Girard and Kagan's reservoir model,^{24a} where the active monomeric homochiral complexes ML_RL_R (or ML_SL_S) (active) and their higher homochiral and heterochiral aggregates (inactive) are taken into account (Scheme 3). The formation of a reservoir of inactive homochiral (*K_m*) and heterochiral (*K_n*) dimeric or oligomeric assemblies with *K_m* < *K_n* will reduce the relative amount of the less abundant enantiomer in the catalytically active species and accordingly result in a positive NLE in the catalysis. In fact, this proposed model can be considered a more sophisticated version of Blackmond's reversible dissociation model,^{24b} with the inactive higher aggregates, (ML_RL_R)_m, playing the same role as the ML_RL_R in the latter, and ML_RL_R and ML_SL_S are active in the present system like the ML_R or ML_S in Blackmond's model.

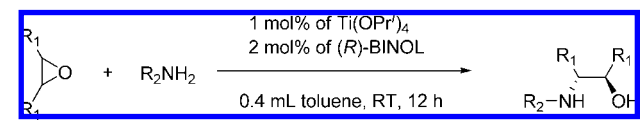
Rationalize the Difference in Reactivity of the Epoxide/Amine Combinations Catalyzed by the Present System. Subsequently, we attempted to extend the scope of the current catalysis by examining the ring-opening reactions between several other couples of amines and epoxides. Although catalytic enantioselective ring-opening of epoxides by the use of amines as the nucleophiles represents a very useful approach to the synthesis of various chiral amino alcohols,⁴⁰ it often suffers from an inherent problem of compatibility (i.e., the possible deactivation of the Lewis acidic catalyst by its irreversible complex formation with the Lewis basic amine and/or with the generated β-amino alcohol).^{21,40a} Perhaps this is the reason that aliphatic amines are rarely successful in the desymmetrization of various meso epoxides, which typically involves the use of aromatic amines (such as aniline or its derivatives) as the nucleophiles. For comparison purposes, the aminolysis of epoxide **1** and cyclohexene oxide (CHO) with benzylamine and aniline,⁴¹ respectively, was examined using BINOL/Ti(O-*i*Pr)₄ (2:1) catalyst, and the results are summarized in Table 2. No reactions were observed for aminolysis of CHO using benzylamine as the nucleophile, which is consistent with Inaba et al.'s observation that several tested monodentate meso epoxides did not undergo the reaction. However, the aminolysis of CHO using aniline proceeded smoothly under similar conditions. These

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(39) (a) Carree, F.; Gil, R.; Collin, J. *Org. Lett.* **2005**, *7*, 1023–1026. (b) Arai, K.; Lucarini, S.; Kobayashi, S. *J. Am. Chem. Soc.* **2007**, *129*, 8103–8111.

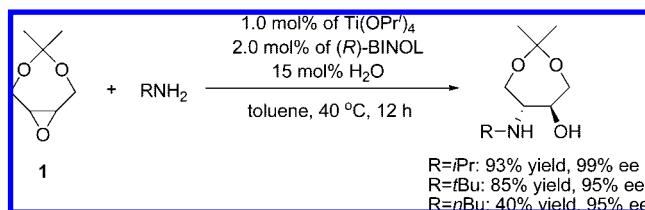
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Table 2. Aminolytic Ring-Opening of Epoxides Catalyzed by BINOL/Ti(O*i*Pr)₄/H₂O System^a

entry	amine	epoxide	yield (%)	ee (%)
1	BnNH ₂	1	96	96
2	BnNH ₂	CHO	no reaction	
3	PhNH ₂	1	no reaction	
4	PhNH ₂	CHO	90	25(35) ^b

^a The reactions were run in the presence of 1 or 5 mol % of BINOL/Ti(O*i*Pr)₄ (2:1) in the presence of water (15 equiv relative to Ti). ^b The value within the parentheses corresponds to the reaction without addition of water under the otherwise identical conditions.

Scheme 4. Enantioselective Ring-Opening Aminolysis of **1** with Aliphatic Amines Using the BINOL/Ti/Water Catalytic System

results, coupled with the good reactivity of the epoxide **1** with benzylamine, suggest that a preferential sequence of coordination power toward the titanium center should exist for the reactants (i.e., epoxide **1** > amino alcohol **3** > BnNH₂ > CHO > PhNH₂). To achieve an adequate activation, the epoxide (**1** or CHO) has to compete with either the aliphatic amine (BnNH₂) or the aromatic amine (PhNH₂) for coordination to the metal site. Here the competitive coordination of the reaction partners (the amine and the epoxide) to the Lewis acidic catalyst seems to be the key factor dictating the reactivity. However, it is not clear at the moment why no reaction was observed between epoxide **1** and the aniline, whereas the similar reaction with benzylamine proceeds efficiently under mild conditions.

Finally, the ring-opening of epoxide **1** using aliphatic amines *n*BuNH₂, *i*PrNH₂, or *t*BuNH₂ proceeded smoothly under the optimized reaction conditions, affording the corresponding amino alcohol products in moderate to high yields with excellent enantioselectivity, irrespective of the steric bulkiness of the alkyl group near the reactive center (NH₂) (Scheme 4). Remarkably, by using the binary ligand catalyst L₁/Ti(O*i*Pr)₄/L₃ (1:1:1) (Chart 1) at a Ti(O*i*Pr)₄ loading of 0.5 mol % under the otherwise identical conditions as above, the product **3** could be obtained in 97% yield with 99% ee in a scale of 50 mmol (12.3 g).

Conclusions

In summary, the mechanism of the asymmetric ring-opening aminolysis of the epoxide **1** catalyzed by the BINOL/Ti/H₂O

system was progressively uncovered on the basis of reaction profile studies, NLE investigation, ¹H NMR and ESI-MS analysis, and the observation of synergistic effect of component ligands in catalysts L_a/Ti/L_b. The titanium species bearing Ti(BINOLate)₂ moiety is unequivocally established as the active species responsible for the catalysis. Apart from the function as a nucleophile, benzylamine also helps to reorganize the catalyst structures and prevent the hydrolytic oligomerization of titanium species. Water is acting as a cocatalyst in the reaction to shuttle the proton between reactants, which represents an unprecedented finding in Ti/diol-mediated catalysis. ESI-MS detection of the catalyst system prepared from a 1:1 *pseudo-racemic* mixture of (*S*)-BINOL and (*R*)-3,3',6,6'-D₄-BINOL indicates the exclusive formation of homochiral Ti((*S*)-BINOLate)₂ and Ti((*R*)-D₄-BINOLate)₂ complexes without appearance of any heterochiral [((*R*)-D₄-BINOLate)Ti((*S*)-BINOLate)] species. Accordingly, the origin of (+)-NLE observed in the present catalytic system is proposed to be caused by the preferential formation of heterochiral aggregates between Ti((*S*)-BINOLate)₂ and Ti((*R*)-BINOLate)₂ species to that of their corresponding homochiral counterparts. Furthermore, the reactivity differences between several couples of epoxide/amine combinations was rationalized on the basis of the arguments on their relative coordination strengths. The results from this study are expected to provide new insights into the often elusive chemistry of Ti(IV)-based catalytic systems, where water or molecular sieves (or alcohols, etc.) are found to play an important yet inexplicable role. Finally, the clarification of the reactivity behavior may help the search for effective asymmetric Ti(IV) catalysts for other types of reactions.

Acknowledgment. Financial support from the National Natural Science Foundation of China (No.20532050, 20423001), the Chinese Academy of Sciences, the Major Basic Research Development Program of China (Grant No. 2006CB806106), the Science and Technology Commission of Shanghai Municipality, and Merck Research Laboratories is gratefully acknowledged. This article is dedicated to Prof. Ryoji Noyori on the occasion of his 70th birthday.

Supporting Information Available: Detailed experimental procedures for (1) the ring-opening aminolysis of the epoxides with amines, (2) reaction profile measurements, (3) NLE study, (4) measurements of ¹H NMR and ESI-MS spectra of catalyst systems, and (5) chiral GC or HPLC analyses of the products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

JA801847R