Titanium-Catalyzed Enantioselective Additions of Alkyl Groups to Aldehydes: Mechanistic Studies and New Concepts in Asymmetric Catalysis

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ABSTRACT

The catalytic asymmetric addition of alkyl groups to aldehydes is an important reaction in the enantioselective synthesis of secondary alcohols. This reaction can be catalyzed by zinc- or titanium-based catalysts. While the mechanism of the zinc/amino alcohol catalysts has received significant attention, the titanium-based catalysts have been less studied. This Account summarizes our mechanistic studies with bis(sulfonamide) and BINOL-derived titanium catalysts. It also describes our use of this reaction in the development of new approaches to asymmetric catalysis, including applications of diastereomeric catalysts and optimization of asymmetric catalysts with achiral and meso ligands.

1. Introduction

The synthesis of organic compounds is ultimately dependent on the formation of carbon−carbon bonds. It is, therefore, clear that the most expeditious route to chiral compounds is one in which a carbon−carbon bond and a stereocenter are formed in a single step with high enantioselectivity. Researchers recognized this 50 years ago, and substantial effort has been put forth to develop methods to promote the asymmetric addition of alkyl groups to aldehydes and ketones. For many years, these investigations were largely unsuccessful due to the highly reactive nature of the organomagnesium and organolithium reagents employed. The breakthrough did not come until 1984, when Oguni[1] discovered that organozinc reagents added enantioselectively to aldehydes in the presence of chiral amino alcohols.[2,3] Extensive mechanistic studies, primarily from the Noyori group with DAIB (Figure 1),[4−8] have greatly contributed to our understanding of the mechanism of reaction.

About the same time that the amino alcohol-catalyzed addition of organozinc reagents was under development, bis(sulfonamide) ligands (Figure 1) were being examined by Yoshioka, Ohno, and Kobayashi for the same transformation.[9,10] These researchers found that the bis(sulfonamide) ligands gave poor enantioselectivities and turnover frequencies (TOF's) when used with dialkylzinc reagents alone; however, when titanium tetraisopropoxide was added, the resulting catalysts proved to be highly enantioselective and exhibited high TOF's (eq 1):

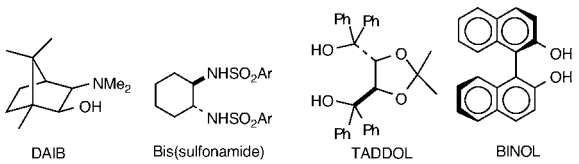


FIGURE 1. Chiral ligands.

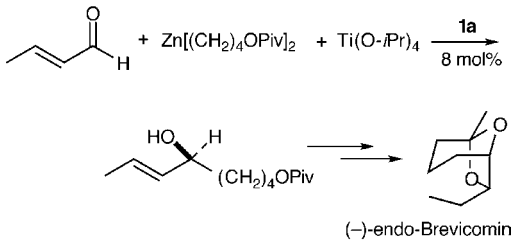
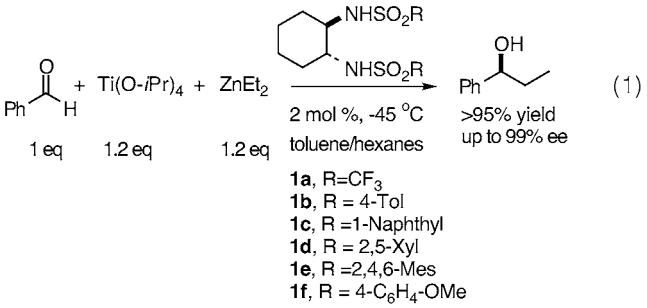


FIGURE 2. Application of bis(sulfonamide)-based catalysts to synthesis.



Similar observations were made by Seebach with TADDOL[11,12] and Chan[13] and Nakai[14] with BINOL (Figure 1).

Significant effort has also been directed toward application of these catalysts to synthesis. Studies by Knochel[15] using functionalized organozincs and aldehydes demonstrated the broad scope of bis(sulfonamide)-based catalysts, including assembly of key intermediates in natural product synthesis (Figure 2).[16]

Our interest in the bis(sulfonamide)-based catalysts was piqued by the mechanisms proposed by Yoshioka, Knochel, and co-workers.[10,17] Their proposed catalyst was a bis(sulfonamido)Ti(O-*i*Pr)$_2$ complex (Figure 3); however, there was no experimental support for the existence of such a species. In fact, no transition metal complexes of bis(sulfonamido) ligands were known at that time.

This Account summarizes our studies of bis(sulfonamide) and BINOL-based catalysts and the use of these systems to develop new approaches to asymmetric catalysis.

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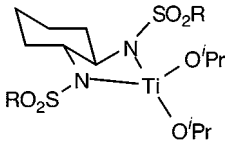
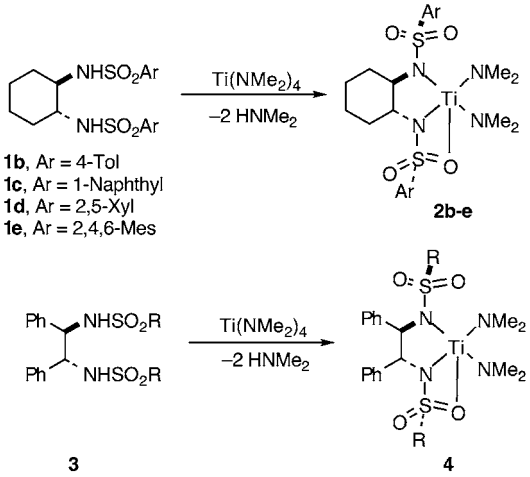


FIGURE 3. Proposed catalyst structure.

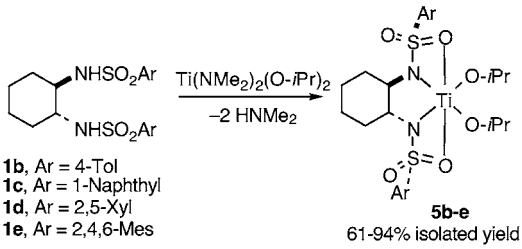
Scheme 1



2. Synthesis and Structure of Bis(Sulfonamido) Titanium Complexes

Our first reactions employed the titanium tetraamide $Ti(NMe_2)_4$ and the bis(sulfonamide) ligands. These reagents reacted rapidly to provide the bis(sulfonamido)-$Ti(NMe_2)_2$ complexes (Scheme 1).[18,19] Simultaneously, Gagné reported synthesis of bis(sulfonamido) complexes **4**.[20]

The bis(sulfonamido)Ti(O-*i*Pr)$_2$ complexes were also synthesized using amine eliminations.[21] Reaction of $Ti(NMe_2)_2$(O-*i*Pr)$_2$ with the bis(sulfonamide) ligands **1b**–**1e** (eq 2) resulted in clean formation of the bis(sulfonamido)Ti(O-*i*Pr)$_2$ complexes. Compounds **5b** and **5e** are highly crystalline solids, and their structures were determined, as exemplified by **5b** (Figure 4).



(2)

The most striking feature of the structures is the tetradentate nature of the bis(sulfonamido) ligands. The Ti–N bond distances, which range from 2.048(3) to 2.083(3) Å, are significantly longer than those of typical titanium dialkyl amides (1.88 Å). These long distances are not surprising given the strong electron withdrawing nature of the sulfonyl group, which renders the nitrogen lone pairs unavailable for donation to titanium. The sulfonyl oxygens are bonded to titanium with Ti–O distances ranging from 2.249 to 2.390 Å. In the (*R*,*R*)-bis-(sulfonamido) ligands, it is the pro-(*R*) sulfonyl oxygens

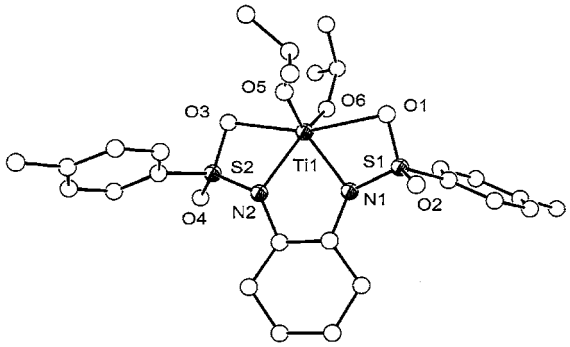
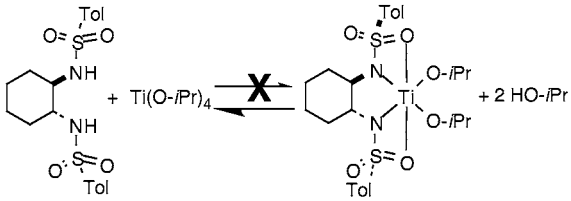


FIGURE 4. Structure of **5b**.

that coordinate to the metal. Coordination of the sulfonyl oxygens renders the sulfurs stereogenic, extending the chiral environment of the bis(sulfonamido) ligand and possibly impacting catalyst enantioselectivity.

3. Mechanistic Studies

With the bis(sulfonamido)Ti(O-*i*Pr)$_2$ complexes in hand, we were positioned to investigate the possible involvement of these species in eq 1. On combination of the bis-(sulfonamide) **1b** with a 5-fold excess of titanium tetra-isopropoxide, however, no reaction was detected (eq 3):



(3)

It appears that the benefit of chelation is not sufficient to overcome the strength of the Ti–O bonds. This result is significant because researchers have attempted to generate bis(sulfonamido)Ti(O-*i*Pr)$_2$ from titanium tetraisopropoxide and bis(sulfonamide) ligands. Under these conditions, however, the bis(sulfonamide) is not bound to titanium. Addition of 2 equiv of 2-propanol to bis-(sulfonamido)Ti(O-*i*Pr)$_2$ (**5b**) resulted in rapid generation of titanium tetraisopropoxide and bis(sulfonamide). The equilibrium in eq 3, therefore, lies far to the left.

The competence of the titanium complexes **5b**–**e** in eq 1 was evaluated by comparing the enantioselectivities using ligands **1b**–**e** to those of complexes **5b**–**e**. Ligands **1b**, **1c**, **1d**, and **1e** gave 1-phenyl-1-propanol with 97%, 90%, 83%, and 18% ee, respectively. Employing compounds **5b**, **5c**, **5d**, and **5e**, under identical conditions, the enantioselectivities were 96%, 92%, 79%, and 19% respectively. These results suggest that complexes **5b**–**e** are catalyst precursors, or possibly the catalytically active species.

Dialkylzinc reagents do react with the bis(sulfonamide) ligands **1b**–**e**.[22–24] It is possible that the equilibrium in eq 3 is established and is driven to the right by reaction of the dialkylzinc reagent with liberated 2-propanol. It is also conceivable that the bis(sulfonamide) reacts first with ZnR_2 and then is transmetalated to titanium.

Table 1. Enantioselectivities and Conversions with Ligands 1b, 1f, and 6a−f (2 mol %) in Equation 1

ligand	**1a**	**1f**	**6a** $n = 6$	**6b** $n = 9$	**6c** $n = 10$	**6d** $n = 12$	**6e** $n = 18$	**6f** $n = 22$
conv. (%) $t = 1$ h	100	100	22	32	40	61	74	97
conv. (%) $t = 3$ h			57	67	71	80	100	100
% ee (config.)	97 (*S*)	98 (*S*)	10 (*R*)	25 (*S*)	19 (*S*)	38 (*S*)	76 (*S*)	89 (*S*)

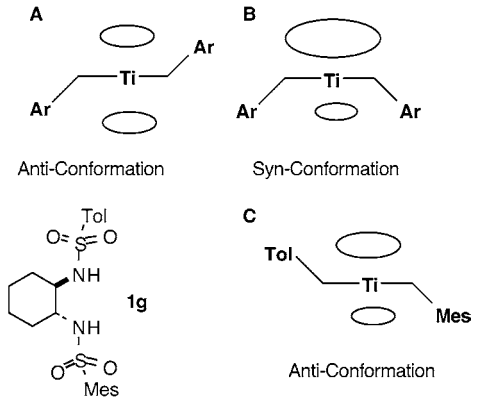


FIGURE 5. Representations of limiting conformations.

4. Examination of the Bis(Sulfonamide) Ligand Conformation in the Active Catalyst[25]

Crucial to understanding the asymmetry transfer in the asymmetric addition reaction (eq 1) is the determination of the role of the sulfonyl oxygens. Coordination of the sulfonyl oxygens to titanium could serve to define a more rigid asymmetric environment and may be important in the transfer of asymmetry. To explore this possibility, it is necessary to determine the conformation of the bis(sulfonamido) ligand in the active catalyst. Two independent approaches, based on structure-enantioselectivity studies, were devised to accomplish this goal.

4.A. Probing Ligand Conformation with Unsymmetric Ligands. Two limiting conformations of the bis(sulfonamido) ligand bound to titanium can be envisioned. The first is the C_2-symmetric conformation of the crystal structures where the aryl groups are anti (Figure 5, structure **A**). To simplify the discussion, the conformations are abbreviated with line structures. In the second limiting conformation, the aryl groups are syn (Figure 5, structure **B**). The C_2-symmetric conformation has two equivalent binding sites on the titanium that are represented by the ovals in Figure 5. In the catalyst formed from ditolyl ligand **1b** (Scheme 1), we would expect these binding sites to be more accessible than those of the dimesityl ligand **1e** since the mesityl groups are larger. In the syn conformation of the ligand (**B**), the two binding sites are inequivalent, with the binding site opposite the aryl rings being the most accessible site for the aldehyde.

We have examined the enantioselectivity and reactivity of catalysts derived from ligands **1b** and **1e**. Under conditions similar to eq 1, the ditolyl ligand **1b** exhibits high TOF (100% conversion, 15 min) and excellent enantioselectivity. Under identical conditions, dimesityl ligand **1e** was 84% complete after 8 h and generated the alcohol in 3% ee. To differentiate between conformations **A** and **B**, we prepared an unsymmetrical ligand containing tolyl and mesityl groups (**1g**, Figure 5). In conformation **C**, the binding sites are inequivalent and operate independently. Therefore, in **C**, the binding site next to the mesityl group will behave like **1e** (slow, low ee), and the site near the tolyl group will behave like **1b** (fast, high ee), dominating the reactivity of **1g**. If conformation **B** predominates, the reactivity of catalyst formed from **1g** would likely lie midway between **1b** and **1e**. In eq 1, ligand **1g** rapidly generated alcohol in 92% ee, suggesting that the ligands are C_2-symmetric in the transition state.[25]

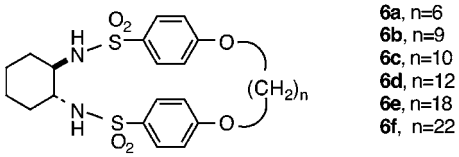


FIGURE 6. Cyclic ligands.

4.B. Conformationally Constrained Ligands.[25] By synthesizing cyclic ligands with short tethers between the aryl groups (Figure 6, **6a**−**f**), the conformation of the ligand is restricted to **B**, Figure 5. If the acyclic ligands were to assume conformation **B**, cyclic ligands with short tethers would show similar enantioselectivities to ligands with longer tethers and acyclic ligands. If the acyclic ligands adopt conformation **A**, ligands with short tethers would exhibit markedly different behavior than those with longer chains.

The reactivity and enantioselectivity of the tethered ligands **6a**−**f** were compared to the nontethered ligands in eq 1 (Table 1). The 4-methoxybenzene derivative (**1f**) was fast and highly enantioselective (98% ee), indicating that electronic effects caused by electron donating OR groups are small.

Cyclic ligands **6a**−**f** were used in eq 1. Ligands with short tethers exhibited low enantioselectivity and TOF's. Increasing the tether length gave higher ee's and TOF's (Table 1), approaching those of the acyclic ligands. These experiments, along with those of the previous section, provide strong support for the C_2-symmetric conformation of the ligand in the transition state.

5. Nonlinear Effects and Alkoxide Exchange Processes

A large body of work describing nonlinear effects in amino alcohol-based catalysts for the asymmetric addition of alkyl groups to aldehydes exists.[3,26] This behavior has been attributed to a monomer−dimer equilibrium of the catalyst. In contrast, reactions employing titanium tetraisopropoxide and TADDOL, BINOL, or most bis(sulfonamide) ligands show a linear relationship between catalyst ee and product ee. Although the titanium-based catalysts are believed to be monomeric, it is surprising that these species do not exhibit changes in enantioselectivity with

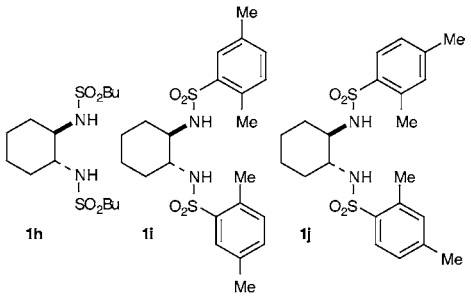


FIGURE 7. Ligands used in nonlinear studies.

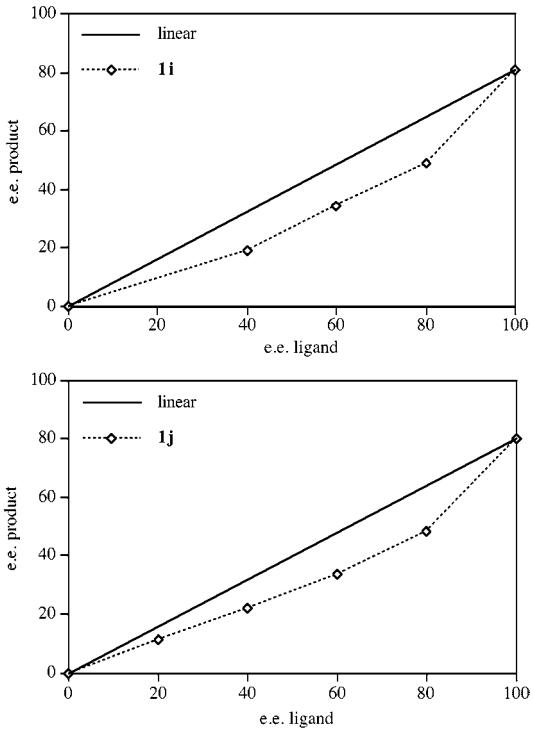


FIGURE 8. Nonlinear effects of ligands **1i** and **1j**.

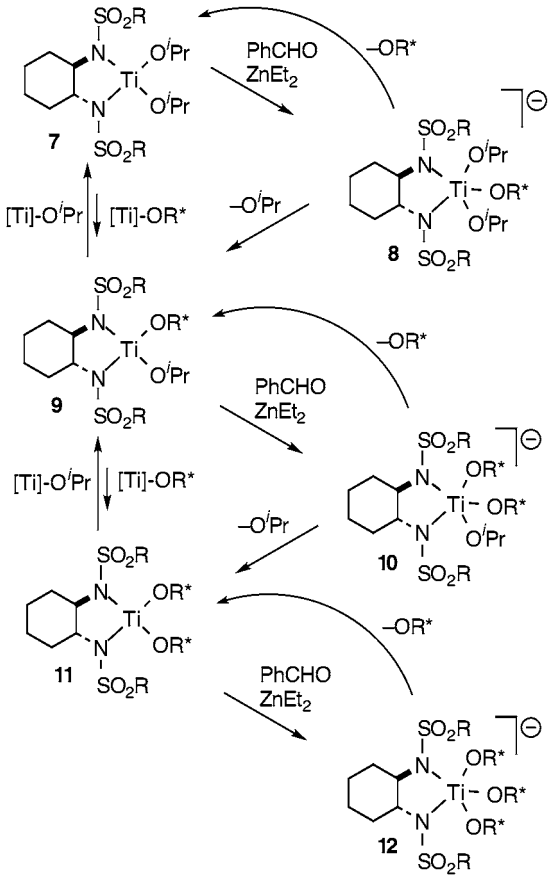
conversion, resulting from autoinduction. Autoinduction arises from the incorporation of the chiral alkoxide product into the titanium catalyst, generating new catalysts that exhibit different enantioselectivities. The lack of autoinduction in titanium based catalysts has been rationalized by rapid exchange of the catalyst-bound chiral alkoxide product with excess titanium tetraisopropoxide.[11]

We initiated a search for bis(sulfonamide) ligands that would exhibit autoinduction because investigations of such a system would allow us to probe alkoxide exchange processes under catalytic conditions. While ligands **1a**, **1b**, and **1h** (Figure 7) were found to exhibit linear behavior, **1i** and **1j** showed negative nonlinear effects (Figure 8). It is noteworthy that the nonlinear effects with ligand **1a** are preparation-dependent.[27]

It was found that the enantioselectivity with benzaldehyde was conversion dependent. The product ee was 72% at low conversion (under 10%) and increased to 80% ee at 100% completion.

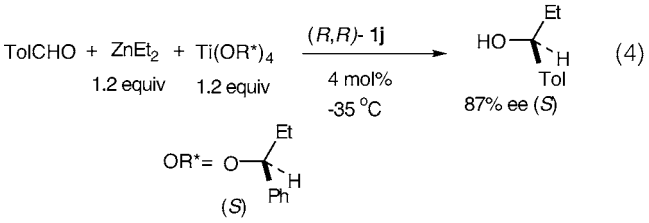
A mechanism consistent with these observations is proposed in Scheme 2. Coordination of aldehyde to the bis(sulfonamido)Ti(O-*i*Pr)$_2$ (**7**) is followed by carbonyl addition to give anionic trialkoxide complex **8**. A [ZnEt]$^+$

Scheme 2. Proposed Mechanism of Autoinduction



or [Ti(O-*i*Pr)$_3$]$^+$ counterion is likely associated with the ate complex but is not shown. Removal of the chiral alkoxide regenerates bis(sulfonamido)Ti(O-*i*Pr)$_2$ (**7**). Loss of an isopropoxy group from **8** forms a new catalyst, bis(sulfonamido)Ti(O-*i*Pr)(OR*), **9**. In a similar fashion **11** is formed. These catalysts are likely to display enantioselectivities and efficiencies different from the original catalyst.

To evaluate how the chiral alkoxide ligands affect the enantioselectivity, (*R*,*R*)-bis(sulfonamido)Ti[(*S*)-OR*]$_2$ was generated using the chiral alkoxide complex Ti[(*S*)-OCH(Ph)Et]$_4$ and the (*R*,*R*)-bis(sulfonamide) ligand **1j**. Use of this complex with 4-methylbenzaldehyde (eq 4)

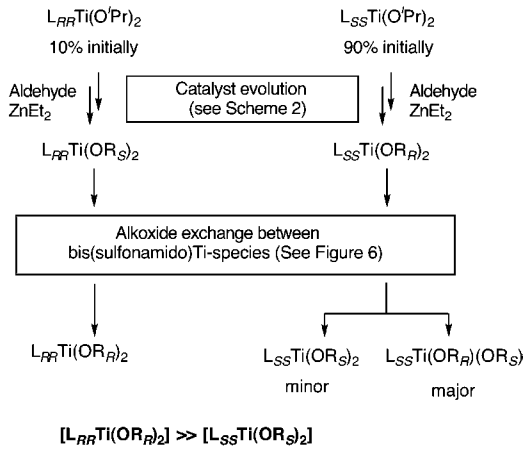


(4)

resulted in product formation of 87% ee, which is higher than that observed beginning with titanium tetraisopropoxide (80% ee), in accord with the proposed autoinduction mechanism.

Further insight into the dynamics of the alkoxide exchange process was gained using nonenantiopure ligand **1j**. Unlike enantiopure **1j**, which resulted in product ee's

Scheme 3. Simplified Catalyst Evolution Scheme



that increased with conversion, nonenantiopure **1j** resulted in ee's that *decreased with conversion*.

This behavior can be understood if alkoxide exchange between bis(sulfonamido)Ti-alkoxide species is much faster than exchange with Ti(O-*i*Pr)$_4$. In Scheme 3, L_{RR} and L_{SS} are the (*R*,*R*)- and (*S*,*S*)-bis(sulfonamido) ligands derived from **1j** and OR_R and OR_S are the (*R*)- and (*S*)-alkoxide products. We hypothesize that the origin of the decreasing enantioselectivity is a result of a thermodynamic preference for the formation the fastest and/or most enantioselective catalyst. As shown in Scheme 3 with (*S*,*S*)-**1j** of 80% ee this faster or more enantioselective catalyst [presumably $L_{RR}Ti(OR_R)_2$] is formed to a greater extent with the *minor* enantiomer of the bis(sulfonamido) catalyst. The major enantiomer of the catalyst, derived from (*S*,*S*)-**1j**, produces the (*R*)-alkoxide product, and therefore, very little (*S*)-alkoxide is present. A proposed transition state for alkoxide exchange is shown in Figure 9.

In summary, methodology has been developed for the synthesis of bis(sulfonamido)Ti(O-*i*Pr)$_2$ complexes, which are likely catalysts or catalyst precursors in eq 1. Reactivity studies indicate that the bis(sulfonamido) ligand adopts a C_2-symmetric conformation in the transition state. It is tempting to attribute this conformational preference to Ti−O(sulfonyl) interactions observed in the solid state; however, no evidence to support this hypothesis exists. Studies with nonenantiopure ligand indicate that autoinduction can play a significant role in product ee and provide insight into otherwise difficult to study alkoxide exchange processes.

6. Investigation into the (BINOLate)-Ti-Catalyzed Addition of Alkyl Groups to Aldehydes

We were attracted to the study of titanium-BINOL catalysts because of the importance of this combination in asymmetric catalysis. Furthermore, the BINOLate-titanium catalyzed asymmetric addition of alkyl groups to aldehydes (eq 5)

developed independently by Chan[13] and Nakai,[14] has become the testing grounds to evaluate the potential of new BINOL-based ligands.

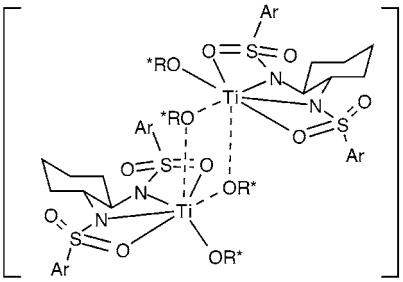
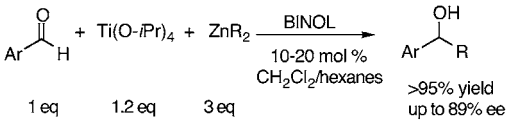


FIGURE 9. Proposed transition state for exchange of chiral alkoxides.



(5)

On the basis of literature precedence and proposals, possible catalysts included monomers (BINOLate)Ti(O-*i*Pr)$_2$ and (BINOLate)Ti(O-*i*Pr)(R), oligomers, the open form of the ligand, with titanium:BINOL of 2:1, and dinuclear species (Figure 10). These compounds each contain an open site, to which the aldehyde might bind.

To model the open form of the catalyst, three monoalkylated BINOL derivatives (**13a**−**c**, Figure 11) were examined in the asymmetric addition reaction. The alkyl group (R) is a surrogate for the second titanium triisopropoxy moiety and does not allow elimination of titanium tetraisopropoxide to generate (BINOLate)Ti(O-*i*Pr)$_2$. X-ray crystal structures of ligands **13a** and **13c** bound to titanium showed no chelation of the ether oxygen to titanium, consistent with solution studies.[28] In comparison with BINOL, ligands **13a**−**c** exhibited much lower TOF's and enantioselectivities (<20%) in eq 5, indicating that the open form is not catalytically active.

6.A. Nonlinear Studies. Nakai had shown that the asymmetric addition reaction (eq 5) did not exhibit nonlinear effects, suggesting that oligomeric [(BINOLate)-Ti(O-*i*Pr)$_2$]$_n$ was unlikely to be an intermediate.[14] Compounds such as trimer [(BINOLate)Ti(O-*i*Pr)$_2$]$_3$ had, however, been characterized in the solid state.[29] We found that employing stoichiometric (BINOLate)Ti(O-*i*Pr)$_2$ in the asymmetric addition with no Ti(O-*i*Pr)$_4$ resulted in nonlinear behavior, suggesting that the Lewis acidic species in the catalytic and stoichiometric reactions were different. Furthermore, the enantioselectivities were determined with several aldehydes and dimethyl- and diethylzinc under catalytic and stoichiometric conditions. Differences in enantioselectivities as large as 85% were observed (Table 2).

Given the propensity of titanium alkoxides to aggregate, we suspected that (BINOLate)Ti(O-*i*Pr)$_2$ was interacting with titanium tetraisopropoxide in the catalytic reactions and with itself in the stoichiometric reactions, consistent with the results of nonlinear studies. This possibility was first examined synthetically.

Addition of two equiv of titanium tetraisopropoxide to racemic BINOL gave X-ray quality crystals of **14** (Figure

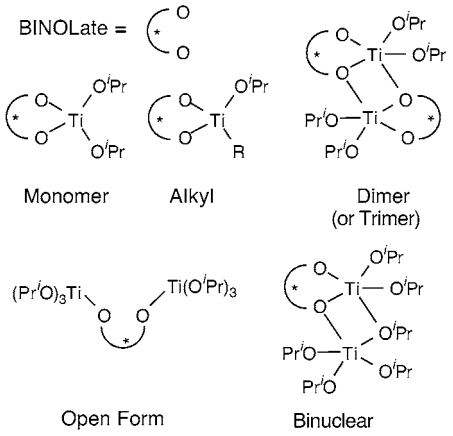


FIGURE 10. Possible intermediates in the asymmetric addition of alkyl groups to aldehydes (eq 5).

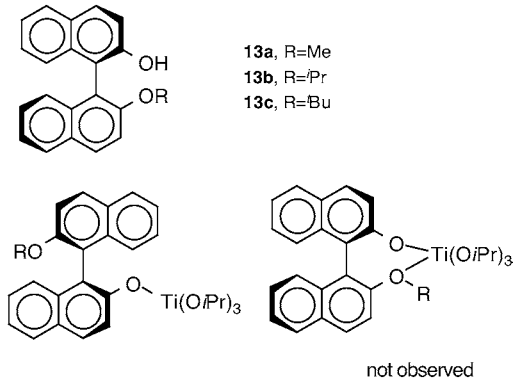
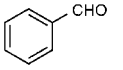
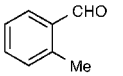
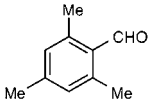


FIGURE 11. Mono alkylated BINOL ligands **13a**−**c** and their possible bonding modes to titanium.

Table 2. Comparison of Product ee's under Catalytic and Stoichiometric Conditions

Aldehyde	Alkyl Source	Stoichiometric (% ee)[a,b]	Catalytic (ee)[c]	Δee[d]
	$ZnMe_2$	65.3	50.2	15.1
	$ZnEt_2$	83.7	88.8	-5.1
	$ZnMe_2$	57.9	18.0	39.9
	$ZnEt_2$	85.2	88.3	-3.1
	$ZnMe_2$	76.0	-7.8	83.8
	$ZnEt_2$	90.2	78.6	11.6

[a] Ratio of (BlNOLate)Ti(O-*i*-Pr)$_2$:aldehyde is 1.00:100. [b] The ee's were measured at low conversion to avoid autoinduction. [c] Ratio of (BlNOLate)Ti(O-*i*-Pr)$_2$:aldehyde is 0.20:1.00. [c] Ratio of (BlNOLate)Ti(O0-*i*-Pr)$_2$:aldehyde is 0.20:1.00. [d] Δee = Stoichiometric ee − catalytic ee.

12) in 70% yield. The solution ^{1}H NMR of **14** indicated that the BINOL to isopropoxy ratio was 1:6. The $^{13}C\{^1H\}$ NMR spectrum contained 20 aromatic resonances, consistent with loss of C_2-symmetry in BINOLate **14**. Use of 6 equiv of titanium isopropoxide relative to BINOL resulted in formation of [BINOLate]Ti(O-*i*Pr)$_2$•[Ti(O-*i*Pr)$_4$]$_2$, **15** (Figure 13). This compound loses an equivalent of titanium tetraisopropoxide when dissolved to generate **14** (NMR).

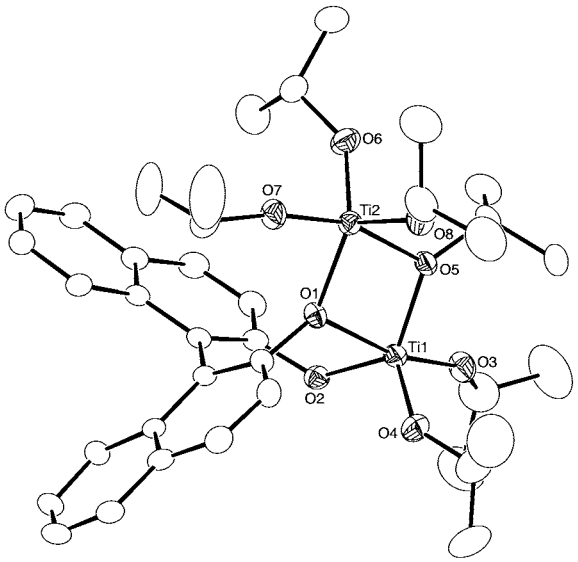


FIGURE 12. Structure of **14**.

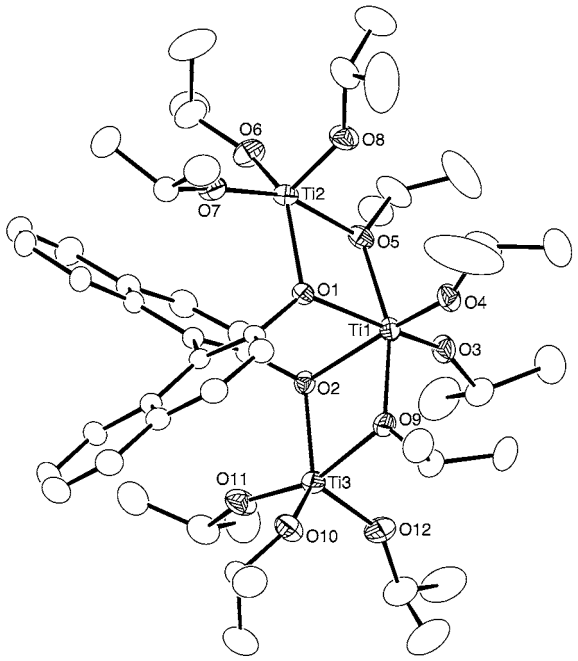


FIGURE 13. Structure of **15**.

The ability of (BINOLate)Ti(O-*i*Pr)$_2$ to bind to titanium tetraisopropoxide inspired us to examine titanium tetraisopropoxide's impact on reaction rates and enantioselectivities. It was found that reactions were faster in the presence of titanium tetraisopropoxide and gave slightly higher enantioselectivities. The titanium tetraisopropoxide alters not only the enantioselectivity of the catalyst but also the rate of the reaction.

6.B. The Role of Dialkylzincs. Seebach proposed that the role of the dialkylzinc reagents in TADDOLate-titanium catalyzed additions to aldehydes is not to add to the aldehyde, but to transfer the alkyl group to titanium.[30] This premise was based on similar trends in enantioselectivities when dialkylzinc reagents were used with titanium tetraisopropoxide compared to use of titanium alkyl species R-Ti(O-*i*Pr)$_3$ generated in situ.[30] Different conditions were necessary with ZnR_2 and R-Ti-

Scheme 4. Asymmetric Reactions with $ZnMe_2$ and Me-Ti(O-*i*Pr)$_3$

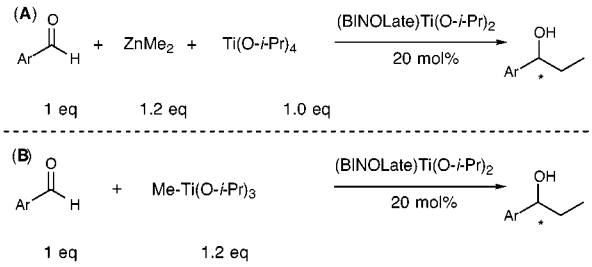
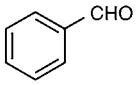
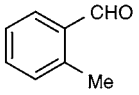
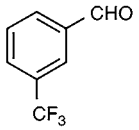
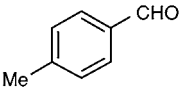


Table 3. Comparison of ee's with $ZnMe_2$ and Me-Ti(O-*i*Pr)$_3$

Aldehyde	Alkyl Source	Ti(O-*i*-Pr)$_4$ (equiv.)	ee
	$ZnMe_2$	1.20	50[a]
	Ti(O-*i*-Pr)$_3$Me	0	49[b]
	$ZnMe_2$	1.20	18[a]
	Ti(O-*i*-Pr)$_3$Me	0	17[b]
	$ZnMe_2$	1.20	59[a]
	Ti(O-*i*-Pr)$_3$Me	0	57[b]
	$ZnMe_2$	1.20	44[a]
	Ti(O-*i*-Pr)$_3$Me	0	42[b]

[a] (BINOLate)Ti(O-^{i}Pr)$_2$:Ti(O-^{i}Pr)$_4$:$ZnMe_2$:RCHO = 0.2:1.2:2.0:1.0. [b] (BINOLate)Ti(O-^{i}Pr)$_2$:Ti(O-^{i}Pr)$_4$:Ti(O-^{i}Pr)$_3$Me:RCHO = 0.2:0:1.2.

(O-*i*Pr)$_3$, however, and the enantioselectivities were sufficiently different that concrete conclusions could not be drawn.

We have addressed this issue by performing two sets of experiments (Scheme 4). In the first (**A**), methyl addition to aldehydes was preformed using dimethylzinc, Ti(O-*i*Pr)$_4$, and 20 mol % (BINOLate)Ti(O-*i*Pr)$_2$ to give product of 50% ee with benzaldehyde substrate (Table 3). In the second (**B**), distilled Me-Ti(O-*i*Pr)$_3$ (120 mol %) was substituted for $ZnMe_2$ as the alkyl group source.

It is known that Me-Ti(O-*i*Pr)$_3$ reacts rapidly with aldehydes to give racemic alcohol on workup.[30,31] We, therefore, performed the reaction with syringe pump addition of Me-Ti(O-*i*Pr)$_3$ over 30 min at 0 °C to limit the concentration of Me-Ti(O-*i*Pr)$_3$ and its uncatalyzed reaction with aldehyde. Under the slow addition conditions, the alkylation of benzaldehyde with Me-Ti(O-*i*Pr)$_3$ gave product with 49% ee (vs 50% ee for the reaction with $ZnMe_2$, Table 3). Three additional aldehydes were examined in Scheme 4 (Table 3). The ee's of the alcohol products were almost identical using $ZnMe_2$/Ti(O-*i*Pr)$_4$ vs Me-Ti(O-*i*Pr)$_3$, clearly demonstrate for the first time that the dialkylzinc reagent is not directly involved in the C−C bond-forming step with the (BINOLate)Ti catalyst. The reactions give the same ee's with and without dimethylzinc and therefore have a common titanium alkyl intermediate. The role of the dialkylzinc reagent is to transfer the alkyl group to titanium.

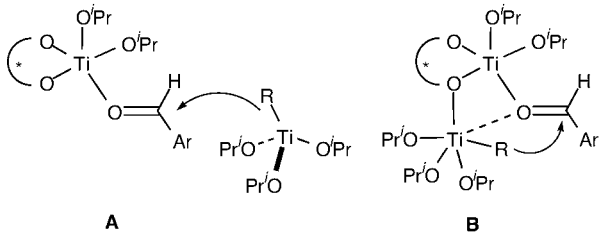


FIGURE 14. Possible transition state for the asymmetric addition reaction.

Furthermore, mixing equal molar amounts of Ti(O-*i*Pr)$_4$ and $ZnMe_2$ in C_6D_6 resulted in formation of 2−3% Me-Ti(O-*i*Pr)$_3$ and MeZn(O-*i*Pr) (NMR), supporting the intermediacy of Me-Ti(O-*i*Pr)$_3$.

6.C. Mechanistic Considerations. Analysis of the above results indicates that two titanium centers are involved in the asymmetric addition. If a common intermediate of the type (BINOLate)TiMe(aldehyde)(O-*i*Pr) were involved in the stoichiometric and catalytic reactions, they would give the same enantioselectivities. As shown in Table 2, this is not the case. Furthermore, it is likely that the methyl group is transferred from (BINOLate)TiMe(O-*i*Pr) in the stoichiometric reactions (in the absence of titanium tetraisopropoxide) and from MeTi(O-*i*Pr)$_3$ in the catalytic reactions. It is conceivable that the nonlinear effects in the stoichiometric reaction with no extra titanium tetraisopropoxide arise because two titanium centers are involved in the carbonyl addition step. One metal activates 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 addition step can have either the same configuration of the ligands or the opposite.

Several related mechanisms can be proposed that are consistent with our results. These range from a direct, bimolecular addition of the alkyl group to the aldehyde bound to (BINOLate)Ti(O-*i*Pr)$_2$ (structure **A**, Figure 14) to the initial formation of a binuclear complex containing the BINOLate ligand, aldehyde and alkyl group (structure **B**). Because of the tendency of the (BINOLate)−titanium complexes to associate, we favor the formation of a binuclear intermediate (**B**).

7. New Approaches to Asymmetric Catalysis: The Use of the Asymmetric Addition Reaction

Given the highly ordered transition state and excellent enantioselectivities of the asymmetric addition reaction, it is the ideal reaction for demonstration of new approaches to asymmetric catalysis.

7.A. Control of Relative Rates with Nondiastereopure Catalysts. Remarkable catalytic processes have been developed in which catalysts of low enantiopurity exhibit very high levels of enantioselectivity through nonlinear behavior.[26] A more complex problem arises in the direct use of nondiastereopure catalysts, where product ee

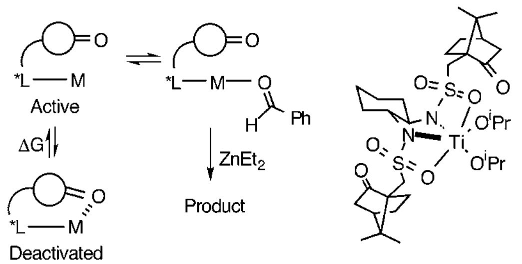
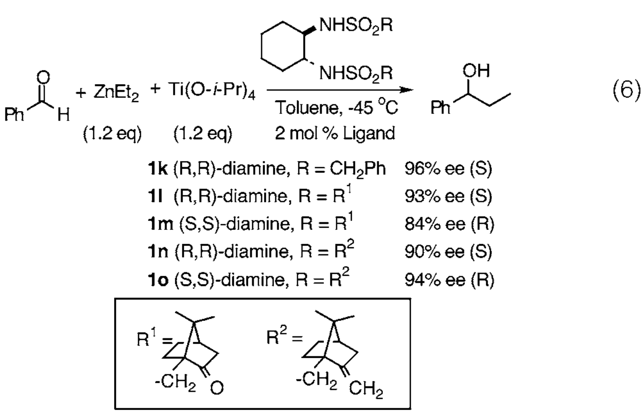


FIGURE 15. The idea of self-inhibiting catalysts.

depends on the enantioselectivity of each diastereomeric catalyst and their relative TOF's.

One possible method to control the TOF's of diastereomeric catalysts would be to inhibit one catalyst to a greater extent than the other.[32] This might be accomplished by incorporation of a chiral substrate analogue into the catalyst's ligand that would bind reversibly to the catalyst. The degree of inhibition would depend on the difference in energy between the bound and unbound states, $\Delta G°$ (Figure 15). The relative concentrations of the active form of the catalysts, which directly impact the TOF's, would then be controlled by the differences in the $\Delta G°$'s for the diastereomeric catalysts ($\Delta\Delta G°$).

We have examined this concept in the context of eq 6:



Use of the (*R*,*R*)-dibenzyl ligand **1k** provided the product (*S*)-1-phenyl-1-propanol in 96% ee. Substitution of the phenyl of **1k** with both enantiomers of a substrate analogue at this remote position would be unlikely to greatly affect the enantioselectivity of the catalyst. We chose the camphorsulfonyl group for this study because coordination of the carbonyl to the titanium in the diastereomeric catalysts should bring the chiral camphor group close to the metal and accentuate the difference in energy of these diastereomeric catalysts (Figure 15).

Examination of diastereomeric ligands **1l** and **1m** in eq 6 indeed showed that there was a minor difference in enantioselectivity between these catalysts [**1l**, 93% ee (*R*), and **1m**, 84% ee (*S*)]. The similarity of the enantioselectivities suggests that the chirality of the camphor group was distant from the bond forming process. We next examined the TOF's of **1l** and **1m** and found that after 15 min, the reaction employing **1l** was 75% complete while reaction with **1m** was only 16% complete.

The large difference in TOF's between **1l** and **1m** was attributed to greater interaction of the camphor carbonyl group in **1m** with titanium. Replacement of the carbonyl oxygens with noncoordinating methylenes would be predicted to provide ligands that form highly enantioselective catalysts with similar TOF's. This is exactly what was observed with ligands **1n** and **1o**, validating the proposed mechanism of catalyst inhibition (eq 6).[33] We were then able to use a 1:1 mixture of the diastereomers **1l** and **1m** (0% diastereomeric excess) and found that the product was generated with 84% enantioselectivity.

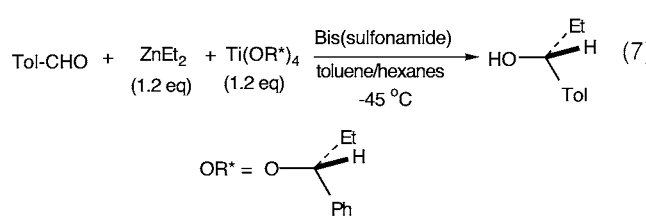
The concept of self-inhibiting catalysts demonstrates that racemic diamine can be used to provide product with high ee.[33] This is particularly important when the chiral portion of the ligand is difficult to resolve. This concept should be applicable to other asymmetric catalysts.

7.B. Optimization of Asymmetric Catalysts with Achiral and meso Ligands. Traditionally, optimization of asymmetric catalysts has been performed by modification of chiral ligands. Some groups have used achiral additives to modify catalyst enantioselectivities,[34−37] and a few have used achiral ligands with chiral conformations to transfer asymmetry.[38−41] We have optimized asymmetric catalysts by variation of large, flexible achiral ligands with chiral conformations.[40]

Screening Achiral and meso Ligands. Our approach to this challenge was to employ small chiral ligands and large, conformationally flexible, achiral and meso ligands that have chiral conformations.[40] The idea relies on the conformational dependency of chiral and achiral or meso ligands bound to a metal. The chiral ligand serves as a source of asymmetry. It interacts with the achiral or meso ligand, causing the latter to preferentially adopt one of the enantiomeric conformations that then defines the chiral environment of the catalyst. Such an interaction serves to transmit and amplify the asymmetry of the chiral ligand.

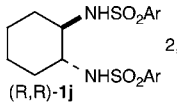
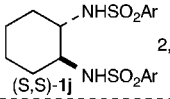
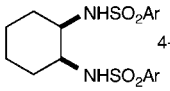
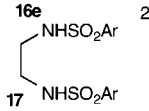
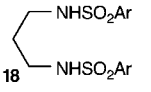
Related strategies have been employed with varying degrees of success; however, as far as we know, this work using chiral titanium alkoxide and achiral or meso bis(sulfonamide) ligands represents the first successful optimization of asymmetric catalysts by screening a variety of achiral and meso ligands that satisfy the requirement of being large and flexible. *In doing so, we observed remarkable changes in the enantioselectivity by over 120%.*[40]

Although diethylzinc does not readily react with aldehydes by itself, the chiral titanium alkoxide (*S*)-Ti(OR*)$_4$ (eq 7) is sufficiently Lewis acidic to promote the addition, which is slow but gives the (*S*)-alcohol in 42% ee. When (*S*)-Ti(OR*)$_4$ was used with the *trans*-bis(sulfonamide) ligands (*R*,*R*)-**1j** and (*S*,*S*)-**1j** (eq 7)



the alcohol product ee's (and configurations) were 84% (*S*) and 81% (*R*) (Table 4). This result indicated that the asymmetry transfer was controlled by the bis(sulfon-

Table 4. Impact of Achiral and Meso Ligand on Enantioselectivities (Equation 7)

Ligand[a]	SO_2Ar Ar=	Conversion (time)	ee (config)
 (R,R)-**1j**	2,4-C_6H_3-Me_2	**11** (15 min)	84 (*S*)
 (S,S)-**1j**	2,4-C_6H_3-Me_2	22 (15 min)	81 (*R*)
 **16a**	4-C_6H_4-CMe_3	62 (15 min)	84 (*R*)
16b	4-C_6H_4-OMe	53 (15 min)	78 (*R*)
16c [b]	2,4-C_6H_3-Me_2	28 (60 min)	32 (*R*)
16d	1-Naphthyl	11 (60 min)	20 (*S*)
16e	2,4,6-C_6H_3-Me_3	7 (60 min)	37 (*S*)
 **17**	4-C_6H_4-CMe_3	16 (60 min)	22 (*R*)
 **18**	4-C_6H_4-CMe_3	16 (60 min)	2 (*R*)

[a] 4 mol % ligand was used unless noted. [b] 10 mol % ligand.

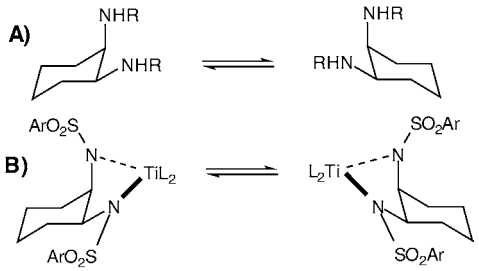


FIGURE 16. (A) The enantiomers of *cis*-1,2-diaminocyclohexane interconvert through ring inversion. (B) Likewise, when L is achiral, the two enantiomers interconvert in a similar fashion. If L is chiral, however, the two titanium complexes are diastereomeric and have different energies (sulfonyl coordination not shown).

amido) ligand and that the chiral alkoxides had little influence on the enantioselectivities.

The most impressive results employed meso bis(sulfonamide) ligands based on *cis*-1,2-diaminocyclohexane. With Ar = 4-*tert*-butylbenzene (**16a**) or Ar = 4-methoxybenzene (**16b**), the (*R*)-alcohol was generated in 84 and 78% ee, respectively [compared to the background which gave the (*S*)-alcohol in 42% ee]. Thus, by adding these achiral bis(sulfonamide) ligands, the change in ee of the alcohol (Δee) with respect to the background reaction was greater than 120%. Ligands with different Ar groups and diamine backbones exhibited lower Δee's (Table 4).

In meso diaminocyclohexane, the two static chair conformations of the free ligand are enantiomers that interconvert by ring inversion (Figure 16). The degenerate conformations of the free ligands become diastereomeric in the coordination sphere of the chiral ligand−metal assembly [Ti(OR*)$_2$] and, thus, have different energies.

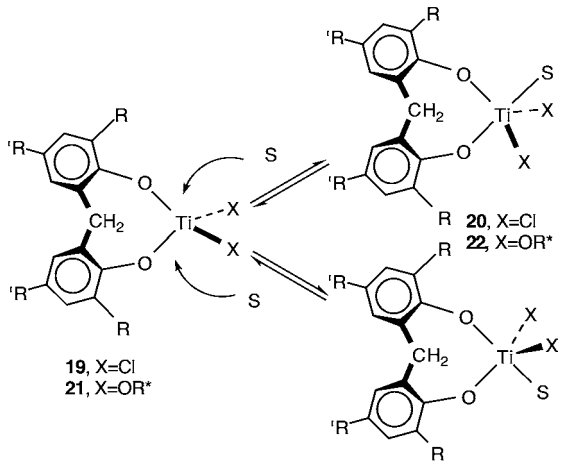


FIGURE 17. When X = Cl and S = THF, coordination of THF leads to two enantiomeric 5-coordinate titanium centers (**20**). When X = OR* and S = aldehyde substrate, the 5-coordinatetitanium complexes (**22**) are diastereomers.

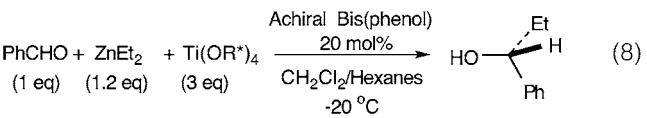
These features make bis(sulfonamide) ligands derived from *meso*-1,2-diaminocyclohexane particularly adept at amplifying the chiral environment.

The use of achiral ligands outlined here is a modular approach to asymmetric catalysis. It involves catalyst modification using combinations of chiral ligands and achiral or meso amplifying ligands and is amenable to facile high throughput screening with numerous reactions.

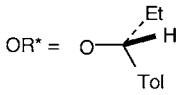
7.C. Metal Geometry-Induced Ligand Asymmetry. Another approach to optimizing asymmetric catalysts with achiral ligands is to use ligands that are symmetric in certain metal geometries but can become asymmetric on binding an additional ligand to the metal.[41]

The 4-coordinate (MBP)$TiCl_2$ [**19**, Figure 17, MBP = methylene bis(phenoxide)] is achiral. Okuda has shown that (MBP)$TiCl_2$ coordinates THF, forming (MBP)$TiCl_2$(THF), in which the MBP oxygens occupy apical and equatorial positions (Figure 17).[42] Due to the inequivalence of the MBP oxygens in (MBP)$TiCl_2$(THF) the (MBP)Ti metallocycle is asymmetric and (MBP)$TiCl_2$(THF) exists as enantiomers.

If it were possible to substitute a substrate for the THF in one of the enantiomers of (MBP)$TiCl_2$(THF), the (MBP)Ti metallocycle would form a chiral environment for the substrate. We set out to examine the possibility of using the asymmetry of the (MBP)Ti metallocycle to influence the relay of chiral information in an asymmetric reaction. To bias the asymmetry of the binding mode of the MBP ligand, we used the chiral alkoxides in eq 8:



(8)



A series of achiral MBP−H_2 derivatives (20 mol %) were combined with Ti(OR*)$_4$ in the asymmetric addition to

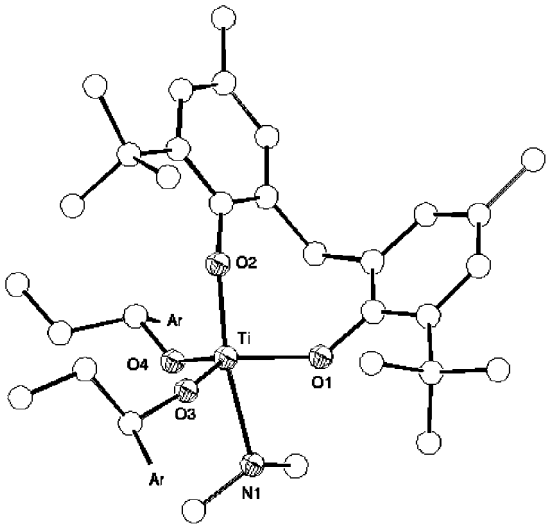
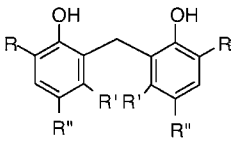


FIGURE 18. Structure of (MBP)Ti(OR*)$_2$(NHMe$_2$).

Table 5. MBP-H$_2$ Ligands 23a−i Used in the Asymmetric Addition of Alkyl Groups to Aldehydes (Equation 8)



ligand	R	R′	R″	t = 1 h ee% (config)
23a	H	H	H	1 (*S*)
23b	H	H	Cl	**9 (*R*)**
23c	Cl	Cl	Cl	24 (*S*)
23d	Me	H	Me	16 (*S*)
23e	Ph	H	H	36 (*S*)
23f	*t*-Bu	H	*t*-Bu	68 (*S*)
23g	*t*-Bu	H	Me	79 (*S*)
23h	*t*-Bu	H	H	73 (*S*)
23i	adamantyl	H	Me	**83 (*S*)**
	no MBP-H$_2$ ligand added			39 (*S*)

aldehydes (eq 8). The results indicated that the achiral MBP ligands had a striking effect on the product ee. When R = adamantyl (**23i**, Table 5), the (*S*)-product was formed with 83% enantioselectivity. In contrast, when R = H 9% enantioselectivity of the (*R*)-alkoxide was observed. *By modifying the achiral MBP ligand, a change in ee of over 90% was observed.*

Substrate coordination can temporarily increase the number of stereocenters in a catalyst. In this system, it is proposed that a change in metal geometry from tetrahedral to trigonal bipyramidal on coordination of a substrate can induce asymmetry in the (MBP)Ti metallocycle (Figure 17). Once in an asymmetric geometry, the (MBP)Ti moiety can participate in, or even control, the relay of asymmetry to the substrate. The asymmetry of the bound MBP ligand is exemplified in the crystal structure in Figure 18, in which the dimethylamine serves as a substrate analogue. On the basis of our results, we predict that catalysts with achiral ligands that become asymmetric when the substrate binds will be more effective in the development and optimization of asymmetric catalysts.

The most remarkable aspect of these two studies on optimization of asymmetric catalysts with achiral and meso ligands is that the chiral ligand, 1-phenyl-1-propoxide, is not a privileged ligand and is not used in modern asymmetric catalyst, because is does not create a useful chiral environment. It is sufficient, however, to bias the asymmetry in the binding of the achiral ligands in Tables 4 and 5 such that they can efficiently transfer asymmetry to the substrate. By using a single enantiomer of an alkoxide and changing meso and achiral ligands from bis(sulfonamides) to MBP, the ee of the product varied from 80% ee (*R*) to 83% ee (*S*). This approach to asymmetric catalysis should be applicable to a variety of catalysts.[43,44]

8. Outlook

Today's best catalysts will inevitably be supplanted. Mechanistic information on these catalysts, however, will remain valuable for the design and development of new catalysts. We have studied the reaction mechanisms of catalysts for the asymmetric addition of alkyl groups to aldehydes by synthesizing and characterizing possible intermediates and applying physical organic techniques. These studies have provided additional pieces of the puzzle that comprise the family of catalytic enantioselective titanium-based addition of alkyl groups to aldehydes.

The mechanistic information gained through these studies has facilitated the application of these reactions to the design of diastereomeric mixture of catalysts, the use of meso and achiral ligands in asymmetric catalysis, and the use metal geometry to induce asymmetry into achiral ligands. We believe that these concepts will be applicable to optimization of future catalysts.

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