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Optimization of Asymmetric Catalysts Using Achiral Ligands: Metal Geometry-Induced Ligand Asymmetry†

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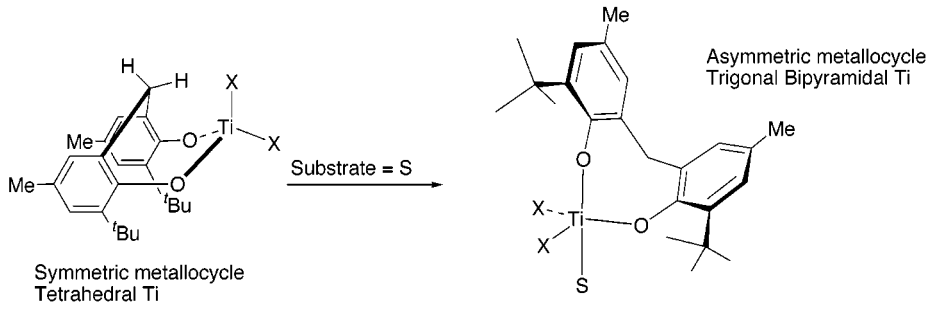
ABSTRACT



Traditionally, asymmetric catalysts have been optimized by modification of resolved chiral ligands. In this Letter, we optimize the asymmetric addition of diethylzinc to aldehydes by modification of *achiral* methylene bis(phenol) ligands. Upon coordination of the substrate, the achiral ligand becomes asymmetric, a concept termed Metal Geometry-Induced Ligand Asymmetry. The enantioselectivity of the catalyst formed from a single resolved ligand and several *achiral ligands* ranged from 9% (*R*) to 83% (*S*).

Various flexible achiral and meso ligands (L) possess chiral conformations.[1] If a metal (M) bearing one such ligand supports a second ligand that is chiral (L*), the conformational preferences of the achiral ligand will be influenced by its interaction with the chiral ligand. The enantiomeric conformations of the unbound achiral ligand (L) become diastereomeric and differ in energy in M(L*)L. If the achiral ligand in a catalyst M(L*)L is in a chiral conformation, it can have an integral, or even a dominant, role in the relay of chiral information to the substrate in an asymmetric process.

Recently published results indicate the effectiveness with which flexible achiral ligands can be used in asymmetric catalysis.[2−10] Pioneering work by Katsuki[2,3] in the asymmetric epoxidation with achiral manganese salen complexes resulted in high enantioselectivities with resolved *N*-oxide ligands.[4] In the first successful report of optimization of an asymmetric catalyst by modification of large, flexible achiral ligands, we demonstrated that variation of *meso* ligands in $M(L^*)_2L$ had a profound impact on the enantioselectivity of the catalyst.[7] Taken together, these results indicate that optimization of asymmetric catalysts can be accomplished through variation of conformationally flexible *achiral ligands* rather than using more costly resolved ligands.

† Dedicated to Professor D. C. Bradley, a pioneer in metal alkoxide chemistry.

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In this Letter we employ a conceptually new approach to the use of achiral ligands in asymmetric catalysis. This concept involves ligands that are symmetric in certain metal coordination geometries but can become asymmetric on binding an additional ligand. We propose that this feature is responsible for the significant changes in the enantioselectivity of the catalyst (from 9% *R* to 83% *S*) in the asymmetric addition of alkyl groups to aldehydes (eq 1). Furthermore, the concept outlined herein is general and potentially applicable to many asymmetric catalysts.

Several groups have used substituted 2,2′-methylene-bis-(phenol) ligands (MBP-H_2 **1**, Figure 1) to prepare polym-

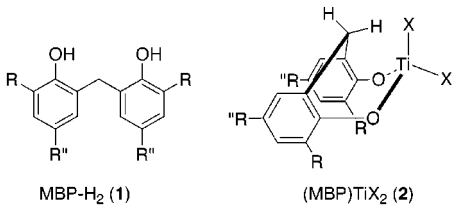


Figure 1.

erization catalysts of the type (MBP)MX_2 with group(IV) metals (Figure 1).[11−16] As illustrated in Figure 1, the MBP ligand in **2** adopts a boat-type conformation in which the methylene hydrogens are inequivalent by NMR spectrometry at room temperature.

The four-coordinate (MBP)$TiCl_2$ (**2**, X = Cl) contains a plane of symmetry and is achiral. Okuda and co-workers have shown that (MBP)$TiCl_2$ coordinated THF, forming (MBP)$TiCl_2$(THF) in which the MBP oxygens occupied apical and equatorial positions (Figure 2).[14]

Because of 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. Similar geometries were reported by Floriani for (MBP)$Zr(BH_4)_2$THF[12] and by Hessen for (MBP)Ti(OTf)(η^2-2-C_6H_4−CH_2NMe_2).[17] We imagined that 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 provide an asymmetric environment for the substrate, differentiating its prochiral faces. Intrigued by this prospect, we explored the possibility of using the metal geometry-induced ligand asymmetry of the (MBP)Ti metallocycle to influence the relay of chiral information in an asymmetric reaction.

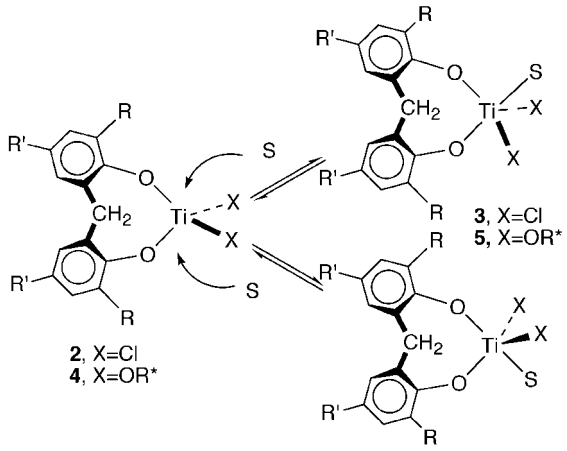
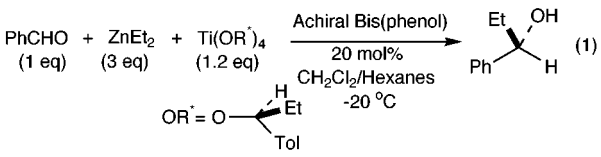


Figure 2. When X = Cl, S = THF, coordination of THF leads to two enantiomeric five-coordinate titanium centers (**3**). When X = OR* and S = aldehyde substrate, the five-coordinate titanium complexes (**5**) are diastereomers.

Our test reaction for this idea was the asymmetric transfer of alkyl groups to aldehydes from diethylzinc.[18,19] This reaction is particularly suitable because it has a highly ordered transition state, making it very sensitive to catalyst modification.[19−24]

In the presence of the resolved alkoxide complex (*S*)-Ti-(OR*)$_4$ [OR* = (*S*)-OCHEt(*p*-Tol)] without any other ligands added, the asymmetric addition resulted in formation of the (*S*)-alcohol with 39% ee (eq 1 and Table 1, entry 13).

A series of achiral derivatives of MBP-H_2 (20 mol %) were combined with Ti(OR*)$_4$ in the asymmetric addition to aldehydes (eq 1). The reactions were run for 40 h (45 to



99% conversion, see the Supporting Information for details); however, ee values are reported at low conversion (5−8%) to avoid complications arising from autoinduction (eq 1, Table 1). Examination of the results indicates that addition of achiral MBP ligands can have a striking effect on the ee of the product [9% (*R*) to 83% (*S*)]. MBP-H_2 ligands with small substituents R gave lower enantioselectivities (entries 1−5). However, it is noteworthy that when R = H the resulting catalysts exhibited considerable differences in

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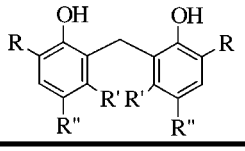
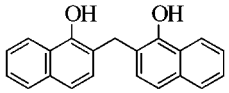
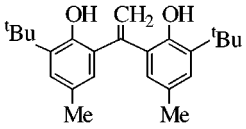
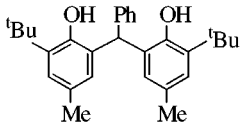
Table 1. 2,2-Methylene Bis(phenol) Derivatives **1a**−**l** (MBP-H2) Used in the Asymmetric Addition of Alkyl Groups to Aldehydes



entry	ligand	R	R'	R"	T=1h ee % (config)
1	**1a**	H	H	H	1 (*S*)
2	**1b**	H	H	Cl	9 (***R***)
3	**1c**	Cl	Cl	Cl	24 (*S*)
4	**1d**	Me	H	Me	16 (*S*)
5	**1e**	Ph	H	H	36 (*S*)
6	**1f**	*t*-Bu	H	*t*-Bu	68 (*S*)
7	**1g**	*t*-Bu	H	Me	79 (*S*)
8	**1h**	*t*-Bu	H	H	73 (*S*)
9	**1i**	Adamantyl	H	Me	83 (*S*)
10	**1j**				28 (*S*)
11	**1k**				45 (*S*)
12	**1l**				60 (*S*)
13	NO MBP-H_2 Ligand added				39 (*S*)

enantioselectivity from that of the background reaction [9% ee (*R*) in entry 2 vs 39% ee (*S*)]. As the size of the R group was increased to *t*-Bu, the enantioselectivities rose markedly (entries 6−8). When R = adamantyl (entry 9), the product ee reached 83%. Substitution in the methylene position (entries 11 and 12) led to a decrease in ee values. (MBP)-Ti(OR*)$_2$ (**5g**) was prepared from **1g**, Ti(O*i*Pr)$_4$, and 2R*OH by removal of the volatile materials and found to be in equilibrium with (MBP)$_2$Ti and Ti(OR*)$_4$.[14] When this mixture was combined with an additional 5 equiv of Ti(OR*)$_4$, as under the reaction conditions, greater than 95% of the MBP ligand was determined to be in (MBP)Ti(OR*)$_2$ (^{1}H NMR). Using an equilibrium mixture of (MBP)Ti(OR*)$_2$, (MBP)$_2$Ti, and Ti(OR*)$_4$ gave slightly higher ee values (83% vs 79% ee in entry 7). The enantioselectivity with **1i** and Ti(OR*)$_4$ (83% at 20 mol % and 87% stoichiometrically) is approaching that of BINOL and Ti(O*i*Pr)$_4$[25,26] (89% ee in our hands).

Our working hypothesis on the mechanism of the chirality relay involving (MBP)Ti complexes is as follows. Four-coordinate **4** (Figure 2) exists as a single enantiomer. Coordination of the substrate (S) can give six trigonal bipyramidal isomers (Figure 3).

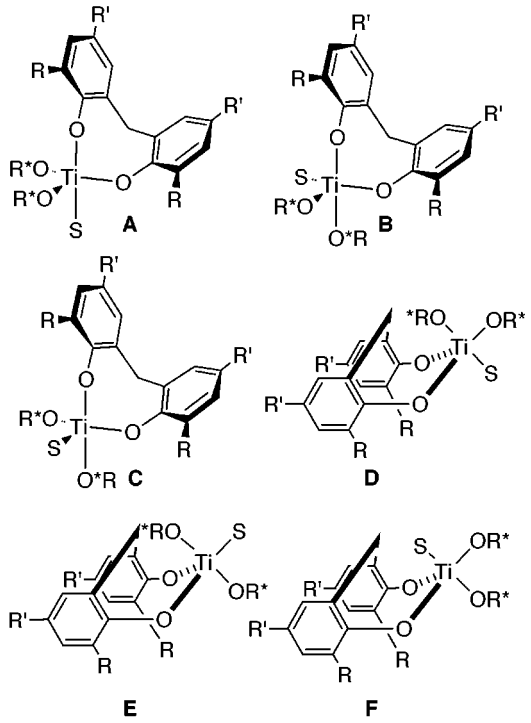


Figure 3. Possible geometries of substrate adducts. Diastereomers which are generated by inversion of the MBP ligand are not shown.

In isomers **A**−**C** the MBP ligand is bound through apical and equatorial positions as in the structures of (MBP)TiCl$_2$-(THF), (MBP)Zr(BH$_4$)$_2$THF, and (MBP)Ti(OTf)(η^2-2-C$_6$H$_4$-CH$_2$NMe$_2$) whereas in **D**−**F** it binds only in the equatorial plane. Investigation into the dynamics of geometrical changes along a reaction pathway in species of this type has long plagued studies in catalysis due to difficulties associated with direct observation of reactive species. This system is no exception, especially given the paucity of information concerning the zinc in these Ti/Zn-based systems.[19]

Nonetheless, examination of possible titanium−aldehyde interactions is informative. In **D**−**F** the MBP ligand is approximately symmetric with respect to the substrate and the chirality would be transferred from just one (**D**, **F**) or two (**E**) proximal chiral alkoxide ligands. In contrast, in geometries **A**−**C** the MBP ligand is asymmetric with respect to the bound substrate. Because of the large impact of the MBP ligand on the ee of the product [from 9% ee (*R*) to 83% ee (*S*)], it is likely that the MBP ligand is directly involved in the transfer of asymmetry to the substrate. We favor coordination geometry **A** based on Okuda's structural determination (Figure 1) and our structure of (MBP)Ti-(OR*)$_2$(NMe$_2$H), **6g**, [OR* = (*S*)-OCHEt(4-C$_6$H$_4$−Cl)] shown in Figure 4. In this complex the HNMe$_2$ is a substrate analogue and is trans to the axial MBP phenoxide oxygen in the distorted trigonal bipyramidal geometry.

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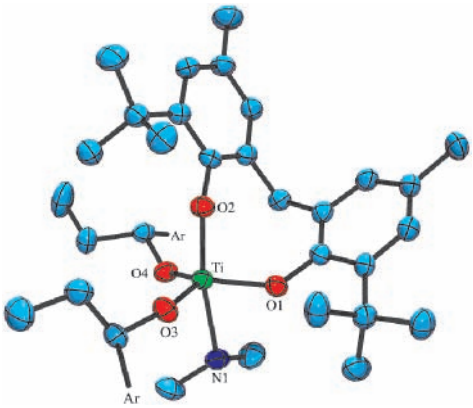

Figure 4. Structure of **6g**. The 4-chlorophenyl groups are omitted for clarity. Bond distances and angles are unexceptional and are located in the Supporting Information.

In summary, substrate coordination can temporarily increase the number of stereocenters in a catalyst.[27,28] 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. Once in an asymmetric geometry the (MBP)Ti moiety can participate in, or even control, the relay of asymmetry to the aldehyde substrate. Furthermore, we propose that catalysts with achiral ligands that become asymmetric when the catalyst binds the substrate will be more effective in the development and optimization of asymmetric catalysts.

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Supporting Information Available: Characterization of ligands, procedures for the asymmetric additions reactions, and details of the structure of **6g**. This material is available free of charge via the Internet at http://pubs.acs.org.

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