Enantioselective Addition of Diethylzinc to Aldehydes Catalyzed by a Titanate Complex with a Chiral Tetradentate Ligand

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The addition of dialkylzincs to aldehydes is one of the most widely studied carbon−carbon bond-forming reactions. Many systems reported to date use amino alcohols as ligands and zinc complexes as catalysts.[1] The asymmetric version of this alkylation reaction can also be catalyzed by chiral titanate complexes[2−4] (e.g., TADDOLs[2] and chiral sulfonamides[3]). We have recently studied a titanate complex with tetradentate helical ligand **1** ((1*R*,2*R*)-(+)-1,2-bis(3,5-dichloro-2-hydroxybenzenesulfonamido)cyclohexane) for the asymmetric addition of diethylzinc to aldehydes (Figure 1).[5] Herein we report the scope of this enantioselective reaction with various substrates. This alkylation approach provides a useful route for the synthesis of some chiral secondary alcohols, especially allylic alcohols,[6] and this work contributes to an understanding of the details of this type of reaction.

Results and Discussion

Using phenolic aromatic sulfonamide **1** as the key cleft-defining group can potentially provide an excellent steric environment to influence the orientation of substrates. Table 1 summarizes the experimental results of asymmetric addition of diethylzinc to various aldehydes. In general, highly enantioselective additions have been realized.

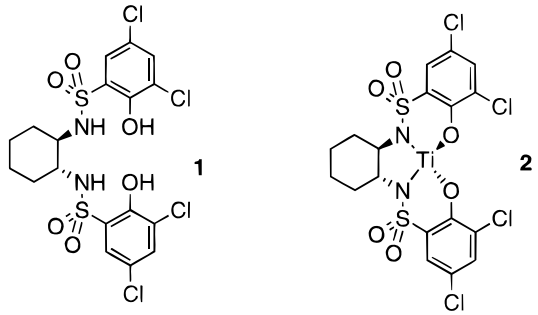

Figure 1.

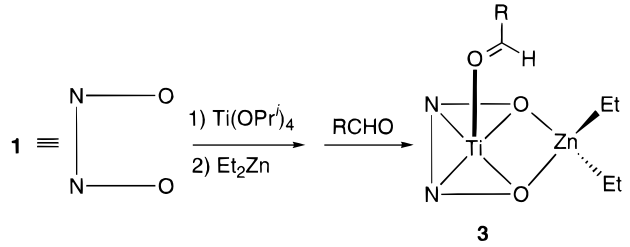

Figure 2.

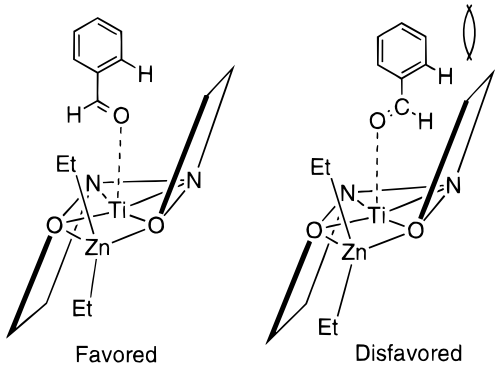

Figure 3.

There have been several different mechanisms proposed for the addition of diethylzinc to aldehydes. We have examined the nature of the titanate complex **2** in the catalytic addition of diethylzinc to aldehydes by NMR spectroscopy and nonlinear asymmetric induction effect.[5] The experimental data suggested that the catalyst containing ligand **1** is a monomeric titanate species during the asymmetric bond forming process. On the basis of our investigation and related mechanistic studies by Seebach,[2] Yoshioka,[3] and Knochel,[4a−k] a plausible key intermediate is the bimetallic complex **3**, which has the dialkylzinc coordinated to the two phenoxide groups prior to the transfer of the ethyl group to the carbonyl (Figure 2). The excess $Ti(OPr^i)_4$ removes the zinc alkoxide from the titanium center.[2] The removal of zinc alkoxide has to be efficient or the catalytic cycle will not continue. This alkylation reaction is a typical ligand-accelerated catalytic process,[7] in which the titanate complex **2** is a better catalyst than $Ti(OPr^i)_4$ alone.

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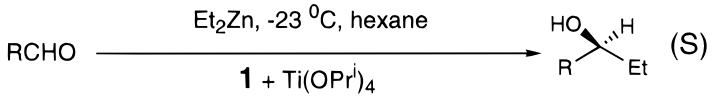
Table 1. Enantioselective Addition of Et_2Zn to Aldehydes Catalyzed by the Titanate Complex of 1



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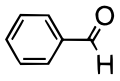
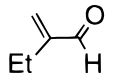
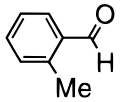
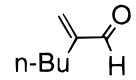
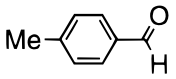
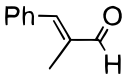
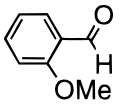
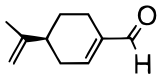
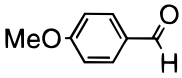
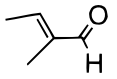
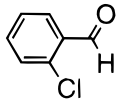
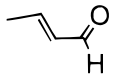
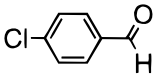
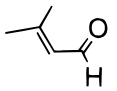
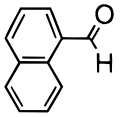
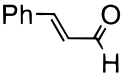
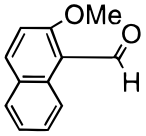
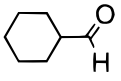
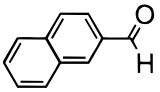
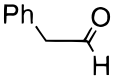
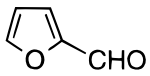
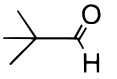
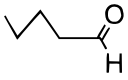
1		**99**	99	13		**94**	99
2		**97**	87	14		**97**	99
3		**93**	93	15		**96**	95
4		75	100	16		89	100
5		**95**	80	17		57	73
6		83	100	18		22	69
7		**99**	95	19		2	75
8		**98**	99	20		75	100
9		3 (R)	60	21		**95**	69
10		**95**	100	22		51	81
11		**90**	67	23		51	81
12		**95**	84	24		11	96

[a] Determined by HPLC using a CHIRALCEL OD column, by GC using a β-DEX column, or by ^{1}H NMR of its Mosher ester. [b] Isolated yield.

On the basis of this model, the enantioselectivity is set when the ethyl group is transferred intramolecularly from zinc to the carbonyl carbon. In the bimetallic complex **2**, the "wall" formed by the two benzene rings is suitable to control enantioselectivity (Figure 3). During the reaction, one of the axial positions is occupied by an aldehyde. The Lewis acidity of the titanium center activates the substrate and accelerates the reaction. The two benzene rings from the ligand generate a chiral environment which limits the free rotation of the sub-

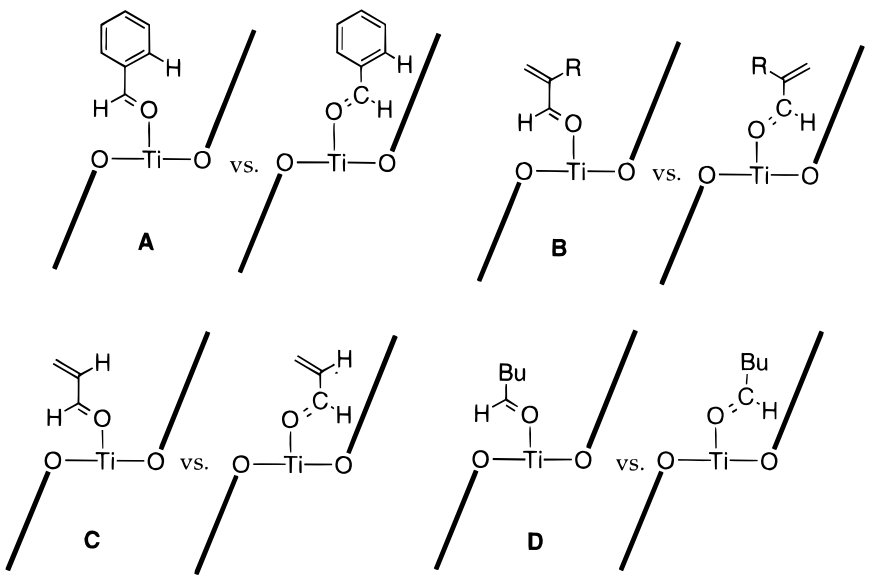


Figure 4. Rationale for asymmetric alkylation of aldehydes.

strates; thus, the *Re* and *Si* faces of benzaldehyde are differentiated (Figure 3). The orientation of benzaldehyde is well controlled with ligand **1**, and the ethyl group can be transferred only to the *Si* face of the substrate. The disfavored interaction between the rigid wall and the aromatic ring of benzaldehyde makes it disfavored for the ethyl group to be transferred to the *Re* face (entry 1 in Table 1).

Using this notion, we have developed a rationale to explain our experimental results (Figure 4). High enantioselectivity was observed with aromatic aldehydes (case **A,** Figure 4) (>90% ee, entries 1−3, 5, 7−8, and 10−11). Introduction of functional groups in the *ortho* position of aromatic aldehydes decreases enantioselectivity (entry 4 vs entry 5; entry 6 vs entry 7; entry 9 vs entry 8). One plausible explanation of this observation is that the *ortho* functional groups can chelate the titanium center and change the transition state geometry (e.g., octahedron). For example, a methoxyl group has a stronger coordinating ability than chloride, which results in a bigger drop in enantioselectivity. In particular, the opposite enantioselectivity was observed when 2-methoxyl-1-naphthyl aldehyde was used as the substrate instead of 1-naphthyl aldehyde. On the other hand, an *ortho* methyl group in the aromatic aldehydes cannot participate in this chelation and high enantioselectivity was obtained (entry 2). Analogous to aromatic aldehydes (case **A**), conjugated aldehydes with α-substitution have the preferred *Si* orientation for the addition of ethyl group (case **B**). High ee's were observed with this type of substrate (entries 12−16). Substitution of hydrogen with an alkyl group in the β position decreases the enantioselectivity (entry 17 vs entry 12). A more dramatic change in the enantioselectivity of addition was demonstrated by removing the α-substituent in the conjugated aldehydes (entry 17 vs entry 18; entry 15 vs entry 20). This decrease may result from the fact that the two orientations of conjugated aldehydes without α-substitution have very little energy difference as illustrated in case **C** in Figure 4. The worst substrate of this family is the one with two β−substituents and without α-substitution (entry 19). High enantioselectivity is generally more difficult to achieve with aliphatic aldehydes than with aromatic aldehydes.[1] However, good to excellent ee's can be obtained with some substituted alkyl aldehydes (entries 20−23). Unbranched aliphatic aldehydes give a low ee (entry 24). The energy difference of the favored and disfavored geometry with linear aliphatic aldehydes is not significant in case **D**.

Our ligand system is similar to Yoshioka's chiral disulfonamides. Yoshioka's[3] and Knochel's[4a−k] study revealed a similar trend of enantioselectivity in diethylzinc addition to aromatic aldehydes, conjugated aldehydes with or without α-substitution, and aliphatic aldehydes. For conjugated aldehydes, α-substitution leads to higher ee and β-substitution leads to lower ee with both catalytic systems.[4c] However, the change in enantioselectivity is larger in our ligand system. This difference may be due to the nature of the titanate complex coordinated by the rigid tetradentate chelating ligand **1**, which cannot adjust its geometry to fit different substrates. Thus, a small change in the substrate structure can lead to a big difference in the enantioselectivity.

Conclusion

A variety of aldehydes have been examined as substrates for Ti-catalyzed enantioselective addition of Et_2Zn in the presence of **1**. High enantioselectivity was obtained with aromatic aldehydes, conjugated aldehydes with α-substitution, and some substituted aliphatic aldehydes. Introduction of *ortho* chelating groups with aromatic aldehydes and removal of α-substituent in conjugated aldehydes decreases enantioselectivity. Linear aliphatic aldehydes are poor substrates for this alkylation reaction. A working model was used to explain this observation. Several useful chiral secondary alcohols can be obtained using this methodology.

Experimental Section

General Information. Unless otherwise indicated, all reactions were carried out under nitrogen. Hexane were freshly distilled from CaH_2. Reactions were monitored by thin-layer chromatographic (TLC) analysis. Column chromatography was performed using EM silica gel 60 (230−400 mesh). Diethylzinc (1.0 M in hexane) was available from Aldrich Co. and used directly. Titanium(IV) isopropoxide was stored under nitrogen. Aldehydes were distilled before use.

^{1}H NMR spectra were recorded on 200, 300, or 360 MHz spectrometers. Chemical shifts are reported in ppm downfield from TMS with the solvent resonance as the internal standard ($CDCl_3$, δ 7.26 ppm). ^{13}C NMR spectra were recorded with complete proton decoupling. Chemical shifts are reported in ppm downfield from TMS with the solvent resonance as the internal standard ($CDCl_3$, δ 77.0 ppm). GC analysis were carried on a Helwett-Packard 5890 gas chromatograph with a 30-m Supelco β-DEX column. HPLC analyses were carried out on a Waters 600 chromatograph with a 25-cm CHIRALCEL OD column.

Experimental Procedure for Enantioselective Addition of Et_2Zn to an Aldehyde. Chiral ligand **1** (0.20 mmol) was added to dry hexane (50 mL), and titanium(IV) isopropoxide (0.42 mL, 1.4 mmol) was added under N_2. The mixture was heated at reflux for 1 h. After the flask was cooled to −23 °C, the diethylzinc (1.8 mmol) was added followed by the aldehyde (1.0 mmol). Stirring was continued at −23 °C for 4 h. HCl (1 M, 10 mL) was added, and the mixture was extracted with ether (3 × 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. The crude product was passed through a silica gel column (eluting with CH_2Cl_2), and the enantioselectivity of the product was measured by HPLC or GC with chiral columns.

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Supporting Information Available: Detailed conditions for the analysis of chiral secondary alcohols (2 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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