

Dramatic catalyst evolution in the asymmetric addition of diethylzinc to benzaldehyde

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Abstract—We have observed product ee's that begin at 20% at low reaction conversion and rise to 79% ee at the completion of the reaction in the asymmetric addition of alkyl groups to benzaldehyde. This rare behavior is attributed to autoinduction, in which the catalyst evolves by incorporation of the product. Based on this, we have been able to optimize the catalyst by variation of achiral, rather than enantiopure ligands. © 2005 Elsevier Ltd. All rights reserved.

1. Introduction

Asymmetric catalysts can evolve over the course of reactions to generate new catalysts that exhibit different properties. This behavior can manifest itself in enantioselectivities that change as reactions progress. One cause of catalyst evolution is the incorporation of the product of the asymmetric reaction into the catalyst. This process is known as autoinduction and was first described by Alberts and Wynberg.^{1,2} Since then, other researchers have reported this behavior.^{3–16}

The observation of autoinduction can provide insight into the mechanisms of asymmetric reactions and, in some cases, expedite the catalyst optimization process. Herein, we report dramatic increases in the product ee's as a function of reaction conversion in the asymmetric addition of ethyl groups to aldehydes. The increase in ee's is attributed to an autoinduction process in which catalyst evolution provides a system that exhibits greatly improved enantioselectivity. Based on a study of this process, we were able to develop a catalyst that exhibited excellent enantioselectivity. The catalyst optimization was performed by variation of achiral ligands^{17–21} rather than enantiopure ligands.

Keywords: Diethylzinc; Titanium tetraisopropoxide; Autoinduction; Bis(sulfonamides).

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2. Results and discussion

Several titanium catalysts have been found to be highly enantioselective in the addition of Et₂Zn to aldehydes. Catalysts derived from TADDOL²² (**1**), BINOL^{23–25} (**2**), and bis(sulfonamide) ligands^{26–33} (**3a**, **3b**, **4**) are widely employed in this reaction (Fig. 1). Studies have demonstrated that most of these catalytic systems generate product of constant ee over the course of the reaction. We recently reported, however, that certain bis(sulfonamide)-based catalysts derived from ligands **3c–3d** do show changes in

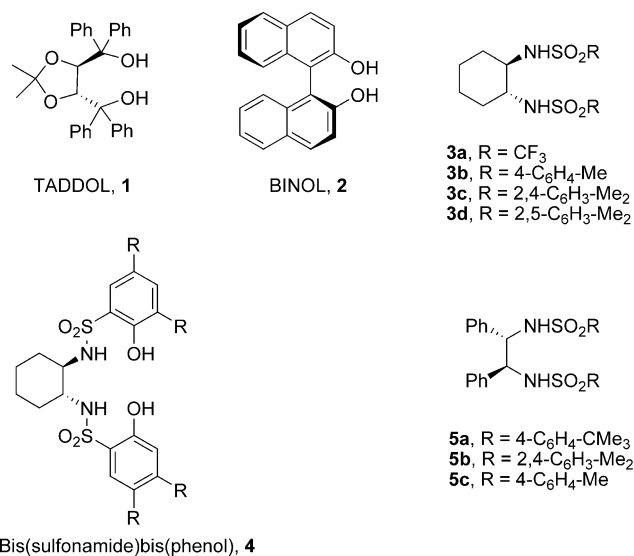
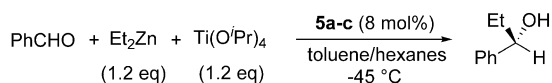


Figure 1. Ligands employed in the asymmetric addition of alkyl groups to aldehydes.



Scheme 1. Diethylzinc addition to benzaldehyde in the presence of bis(sulfonamide) ligands derived from stilbene diamine.

enantioselectivity of 8% over the course of the reaction (Scheme 1). We postulated that this behavior was due to autoinduction, which was supported by mechanistic studies and the observation of nonlinear behavior.³⁴

During our studies of the mechanism of the asymmetric addition of alkyl groups to aldehydes promoted by bis(sulfonamide)-based catalysts (Scheme 1) we found that catalysts prepared from stilbene diamine (**5a–c**, Fig. 1) exhibited large changes in product ee with conversion. Employing 8 mol% of **5a** in Scheme 1 and following the reaction by removal of aliquots and analysis we observed that the ee was 20% at around 10% conversion. As the reaction proceeded, however, the ee rose rapidly to a maximum 79% at 100% conversion. These results are illustrated in Figure 2, curve A. In this reaction, the enantioselectivities of the catalysts generated at higher conversion must be greater than the final ee of 79%. The use of catalyst **5c** led to a similar, but smaller, increase in the ee of the product over time. Interestingly, catalyst **5b** initially gave the (*R*)-enantiomer of the product with an enantioselectivity of 18%. As the reaction progressed, however, the sense of the enantioselectivity switched and the (*S*)-enantiomer predominated with an ee of 27% (Fig. 2, curve B).

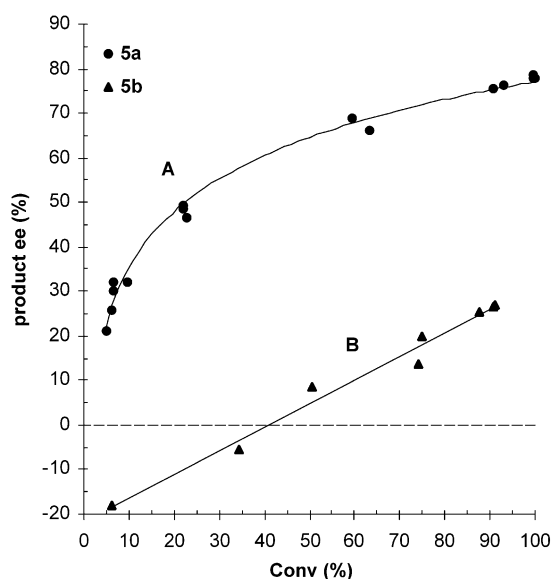
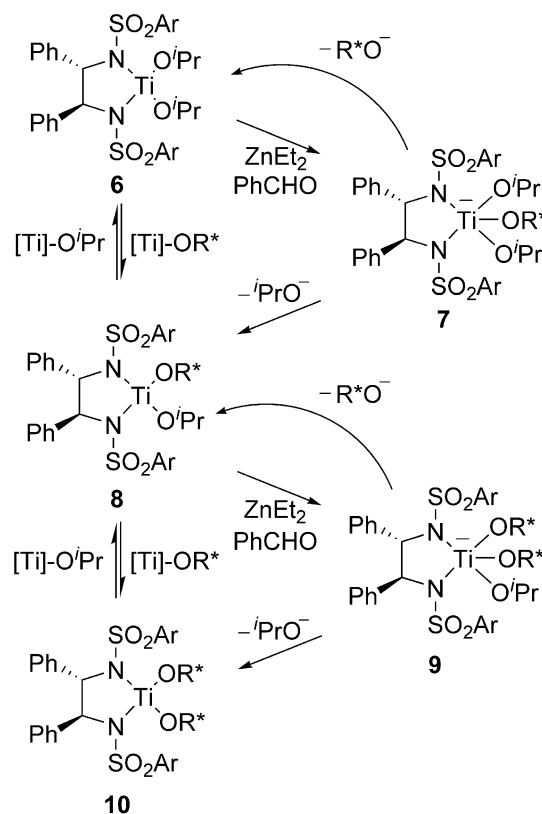


Figure 2. Plot of ee (%) vs conversion (%) with ligands **5a–b** (Scheme 1).

To explain the results in Figure 2, we propose a mechanism involving catalyst evolution (Scheme 2). The initial catalyst for this reaction is proposed to be $\text{L}^*\text{Ti}(\text{O}^i\text{Pr})_2$, **6**, [$\text{L}^* = \text{bis}(\text{sulfonamido})$].^{26–29} We envision that the aldehyde is first activated by coordination to the titanium center and the ethyl group is delivered. It is not known which metal is responsible for delivery of the ethyl group in this system, the zinc or the titanium. In related systems, the organozinc has



Scheme 2. Proposed mechanism of catalyst evolution.

been found to undergo transmetalation with titanium to give $\text{MeTi}(\text{O}^i\text{Pr})_3$ and it is titanium that is responsible for delivery of the methyl to the aldehyde carbonyl.^{35,36} Addition of the ethyl group to the aldehyde is proposed to give an intermediate complex (**7**) containing three alkoxides bonded to titanium. To regenerate the proposed catalyst, one of the alkoxide groups must be removed from **7**, where OR^* is the alkoxide formed by ethyl addition to benzaldehyde. Removal of the chiral alkoxide (R^*O^-) regenerates the initial catalyst, **6**, while loss of ($i\text{PrO}^-$) affords two new diastereomeric catalysts (**8**) where R^*O^- has the (*S*)-configuration (major) or the (*R*)-configuration. Likewise, addition promoted by $\text{L}^*\text{Ti}(\text{O}^i\text{Pr})(\text{OR}^*)$, **8**, can generate three diastereomeric $\text{L}^*\text{Ti}(\text{OR}^*)_2$ catalysts (**10**). These new catalysts will likely have different activities and enantioselectivities from the initial catalyst **6**.

The issue of alkoxide exchange is of fundamental importance in a number of enantioselective processes.^{37–39} The proposed mechanism in Scheme 2 requires that alkoxide exchange between $\text{Ti}(\text{O}^i\text{Pr})_4$ and catalysts bearing chiral alkoxide groups be slow relative to the asymmetric addition. If this exchange process were fast, the distribution of alkoxide ligands would be under equilibrium control. The concentrations of $\text{L}^*\text{Ti}(\text{OR}^*)_2$ and $\text{L}^*\text{Ti}(\text{OR}^*)(\text{O}^i\text{Pr})$ would, therefore, be low due to the high ratio of isopropoxide ligands to chiral alkoxide ligands (4.8:1 at the end of the addition reaction). In the fast alkoxide exchange scenario, it would be unlikely to observe the high degree of autoinduction necessary for the changes in product ee outlined in Figure 2.

because it does not revolve around the synthesis and screening of chiral ligands, which is often an arduous task.

4. Experimental

4.1. General procedures

All manipulations involving titanium alkoxides and diethylzinc were carried out under an inert atmosphere in a Vacuum Atmospheres dry box with attached MO-40 DriTrain, or by using standard Schlenk or vacuum line techniques. Solutions were degassed as follows: they were cooled to $-196\text{ }^{\circ}\text{C}$, evacuated under high vacuum, and thawed. This sequence was repeated three times in each case. ^1H NMR spectra were obtained on a Bruker 360-MHz Fourier transform NMR spectrometer at the University of Pennsylvania NMR facility. ^1H NMR spectra were recorded relative to residual protiated solvent. Chemical shifts are reported in units of parts per million relative to tetramethylsilane and all coupling constants are reported in Hz. Unless otherwise specified, all reagents were purchased from Aldrich Chemical Co. and used without further purification. Titanium tetraisopropoxide, benzaldehyde, 4-methylbenzaldehyde, (*S*)-1-phenyl-1-propanol and (*S*)-1-tolyl-1-propanol were distilled under vacuum and stored in glass vessels sealed with Teflon stoppers. Et_2Zn (1.0 M in toluene) and titanium alkoxides (in hexanes) solutions were prepared in the dry box and stored in Schlenk storage tubes under nitrogen. The following compounds were prepared by literature procedures: (*1S,2S*)-(-)-1,2-diphenylethylenediamine,⁴⁴ 2,4-dimethylbenzenesulfonyl chloride,²⁰ bis(sulfonamide) ligands **5a–c**,^{44,45} $\text{Ti}[(\text{S})\text{-OCH}(\text{Tol})\text{Et}]_4$,²⁰ and $\text{Ti}(\text{NMe}_2)_2\text{Cl}_2$.⁴⁶ Tetrakis(cyclohexyloxy)titanium and tetrakis(cycloheptyloxy)titanium were prepared by mixing of titanium tetraisopropoxide and 4 equiv of cyclohexanol or cycloheptanol, respectively, in toluene, and subsequent azeotropic removal of $i\text{PrOH}$ with toluene. Hexanes (UV grade, alkene free) was distilled from sodium benzophenone ketyl/tetraglyme under nitrogen. Toluene, pentane and diethylether were distilled from sodium benzophenone ketyl under nitrogen. Deuterated solvents (purchased from Cambridge Isotopes) for use in NMR experiments were dried in the same manner as their protiated analogs, but were vacuum transferred from the drying agent. CDCl_3 was dried over calcium hydride and vacuum transferred.

Enantiomeric excesses were determined using GC methods. GC-analyses were carried on a Hewlett–Packard gas chromatograph with a 30-m Supelco $\beta\text{-DEX}^{\text{TM}}$ column.

4.2. General procedure for the asymmetric alkylation of benzaldehyde using chiral bis(sulfonamide) ligands and titanium tetraisopropoxide

The chiral bis(sulfonamide) **5** (0.11 mmol, 8 mol%) was introduced in a dry Schlenk flask, and the system was purged with nitrogen. Diethylzinc (1.7 mL, 1.0 M in toluene, 1.2 equiv) was added and the mixture cooled to $-45\text{ }^{\circ}\text{C}$. After 10 min, titanium tetraisopropoxide (1.2 mL, 1.4 M in hexanes, 1.2 equiv) was slowly added to the mixture. Stirring was continued for 10 min and benzaldehyde (0.14 mL, 1.38 mmol, 1.0 equiv) was added. The

reaction was sampled at different times by carefully removing aliquots and quenching them with 2 N HCl. The aqueous layer was extracted with pentane and the resulting solutions were analyzed by GC (Supelco SPB-5, 30 m \times 0.25 mm, 115 $^{\circ}\text{C}$, 1.3 mL/min). (*S*)-1-phenylpropanol: 16.0 min; (*R*)-1-phenylpropanol: 16.9 min).

The asymmetric alkylations of benzaldehyde mediated by other titanium alkoxides were performed analogously. In the case of tetrakis(cyclohexyloxy)titanium and tetrakis(cycloheptyloxy)titanium the concentrations of the titanium alkoxide solutions used were 0.7 and 1.0 M, respectively.

4.2.1. Preparation of $\text{Ti}(\text{NMe}_2)_2[\text{O}-((\text{S})\text{-CHPh}(\text{Et}))_2]$. (*S*)-1-phenylpropanol (203 mg, 1.49 mmol) was dissolved in Et_2O (5 mL) in the dry box and BuLi (0.6 mL, 2.49 M in hexanes, 1.49 mmol) was added. After 10 min at rt, a solution of $\text{Ti}(\text{NMe}_2)_2\text{Cl}_2$ (155 mg, 0.75 mmol) in Et_2O (1 mL) was added and the reaction mixture was stirred for 3 h. $\text{Ti}(\text{NMe}_2)_2[\text{O}-((\text{S})\text{-CHPh}(\text{Et}))_2]$ (302 mg, 99%) was obtained as a light brown oil and used without further purification. The ^1H NMR spectrum (C_6D_6) of this compound showed it to be a mixture of different compounds of formula $\text{Ti}(\text{NMe}_2)_n(\text{OR}^*)_{4-n}$.

4.2.2. Preparation of **11.** $\text{Ti}(\text{NMe}_2)_2[\text{O}-((\text{S})\text{-CHPh}(\text{Et}))_2]$ (81 mg, 0.20 mmol) and bis(sulfonamide) ligand **5c** (101 mg, 0.19 mmol) were combined in pentane (3 mL), resulting in an orange suspension. After stirring for 36 h at rt, the undissolved ligand was filtered and the filtrate was concentrated under vacuum to yield a white solid (138 mg, 85%). X-ray crystals were grown over several days by slow diffusion of hexanes into a CH_2Cl_2 solution of crude **11**. ^1H NMR (360 MHz, C_6D_6): δ 1.19 (t, $J=7.3$ Hz, 6H), 1.87 (s, 6H), 2.06 (m, 2H), 2.16 (m, 2H), 5.16 (s, 2H), 6.01 (t, $J=6.4$ Hz, 2H), 6.50 (d, $J=7.4$ Hz, 4H), 6.57 (t, $J=8.3$ Hz, 4H), 6.69 (t, $J=7.1$ Hz, 2H), 6.85 (d, $J=7.8$ Hz, 4H), 7.14 (t, $J=6.9$ Hz, 2H), 7.23 (t, $J=7.2$ Hz, 4H), 7.63 (d, $J=7.8$ Hz, 4H), 7.71 (d, $J=7.5$ Hz, 4H).

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