Synthesis and Crystal Structures of Bis(sulfonamido) Titanium Bis(alkoxide) Complexes: Mechanistic Implications in the Bis(sulfonamide) Catalyzed Asymmetric Addition of Dialkylzinc Reagents to Aldehydes

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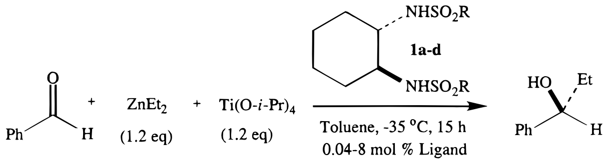
The enantioselective formation of C−C bonds is an area of intense research effort.[1−6] Examples involving the addition of organometallic reagents to carbonyl groups have proven to be the most successful of this broad class of reactions. The addition of dialkylzinc reagents to aldehydes in the presence of chiral Lewis acid catalysts have been reported to give excellent enantioselectivities.[7] The most successful catalysts in these reactions have been titanium complexes which employ chiral diol[8−11] or bis(sulfonamide)[12−14] based ligand systems. The bis(sulfonamide) ligands, which were introduced by Ohno,[12−14] have been effectively applied to the synthesis of highly functionalized secondary alcohols by Knochel[15−20] (eq 1).



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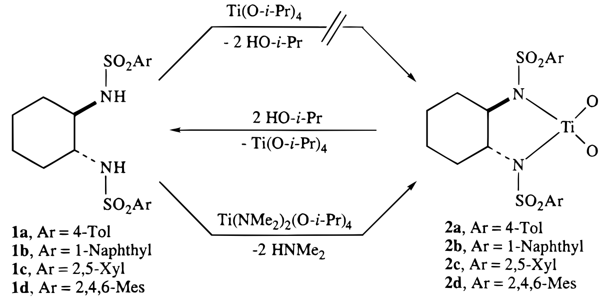
Although a wide variety of dialkylzinc reagents and aldehydes have been employed, the mechanism of this process has not been adequately explored. It has been proposed[12−14,21] that the asymmetric reaction involves the initial formation of the chiral titanium complexes **2a**−**d** shown in Scheme 1 or their dimers.[22] In this Communication we report the independent synthesis and structural determination of these unique complexes and demonstrate their involvement in the asymmetric addition reaction (eq 1).

Scheme 1



The first step in the asymmetric addition reaction is proposed to involve ligand exchange between the bis(sulfonamide) ligands **1a**−**d** and titanium tetraisopropoxide to give **2a**−**d** (Scheme 1). However, on combination of **1a** with a 5-fold excess of titanium tetraisopropoxide in $CDCl_3$, *no reaction was detectable* by ^1H NMR spectrometry (500 MHz). This result prompted the search for an alternative method for the synthesis of these complexes.[23]

We were attracted to titanium amides as precursors to **2a**−**d** due to the polar nature of the Ti−NR$_2$ group.[24] Combination of **1a**−**d** with the mixed amide alkoxide complex[25,26] Ti(NMe$_2$)$_2$(O-*i*-Pr)$_2$ resulted in the clean formation of **2a**−**d** in 94−61% yield (Scheme 1). X-ray quality crystals of **2a** and **2d** were obtained from diethyl ether. An ORTEP diagram of **2a**[27] is shown in Figure 1, while that for **2d**[28] is very similar and not shown. The most striking feature of the structures is the tetradentate nature of the ligand which is coordinated through the sulfonyl oxygens and the sulfonamido nitrogens. 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 less available for donation to the titanium center.[29,30] The sulfonyl oxygens are bonded to the titanium center with Ti−O distances

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(27) **X-ray data for 2a**: Data were collected at 192 K using highly oriented graphite crystal monochromated Mo Kα radiation. There were 5573 reflections collected in the 2θ range 3.0−50.0° of which 5243 were unique ($R_{int} = 2.15\%$). The structure was solved by direct methods, and non-hydrogen atoms were refined anisotropically. In the final least-squares refinement cycle on F, R = 5.59%, R_w = 7.01%, and GOF = 1.48 for 3643 reflections with $F > 4.0\sigma(F)$ and 338 parameters. The crystal data are $a = 10.217(5)$ Å, $b = 11.769(5)$ Å, $c = 13.293(7)$ Å, $\alpha = 78.21(4)°$, $\beta = 74.23(4)°$, $\gamma = 79.12(4)°$, $V = 1490.6(14)$ Å^3, space group P-1, $Z = 2$, MW = 586.6, and ρ(calcd) = 1.307 g/cm^3.
(28) **X-ray data for 2d**: Data were collected at 197 K using highly oriented graphite crystal monochromated Mo Kα radiation. There were 6203 reflections collected in the 2θ range 3.0−50.0° of which 5903 were unique ($R_{int} = 1.18\%$). The structure was solved by direct methods and non-hydrogen atoms were refined anisotropically. In the final least-squares refinement cycle on F, R = 5.26, R_w = 6.67%, and GOF = 1.39 for 4128 reflections with $F > 4.0\sigma(F)$ and 387 parameters. The crystal data are $a = 10.164(4)$ Å, $b = 12.231(5)$ Å, $c = 14.015(7)$ Å, $\alpha = 93.71(4)°$, $\beta = 101.77(3)°$, $\gamma = 99.65(3)°$, $V = 1672.7(13)$ Å^3, space group P-1, $Z = 2$, MW = 641.7, and ρ(calcd) = 1.274 g/cm^3.
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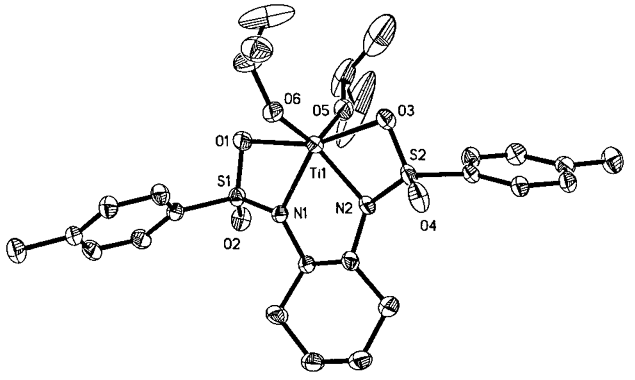

Figure 1. Crystal structure of **2a**. Selected bond distances (Å) are as follows: Ti(1)−O(1) = 2.354(3), Ti(1)−O(3) = 2.264(3), Ti(1)−O(5) = 1.758(3), Ti(1)−O(6) = 1.778(4), Ti(1)−N(1) = 2.047(5), Ti(1)−N(2) = 2.060(4).

ranging from 2.249(3) to 2.390(3) Å. The coordination of the titanium-sulfonyl oxygens maintains a rigid C_2-symmetric environment and may be an important factor in the transfer of asymmetry.

The competence of the titanium complexes **2a**−**d** in the asymmetric addition reaction (eq 1) was evaluated by comparing the ee of the 1-phenyl-1-propanol produced using the ligands **1a**−**d** to the ee of the alcohol produced using the complexes **2a**−**d**. Using the procedure of Ohno, the ligands **1a**−**d** gave 1-phenyl-1-propanol with enantiomeric excesses of 97, 90, 83, and 18% respectively. Employing compounds **2a**−**d**, under identical reaction conditions, the enantioselectivities were determined to be 96, 92, 79, and 19% respectively. These results suggest that complexes **2a**−**d** are catalyst precursors or possibly the catalytically active species. Reexamination the equilibrium of the bis(sulfonamide) ligand and titanium tetraisopropoxide was performed by addition of 2 equiv of dry 2-propanol to complex **2a** in $CDCl_3$. On combination, quantitative formation of the ligand **1a** and titanium tetraisopropoxide (Scheme 1) was observed (^1H NMR).

From this result, it is clear that the complexes **2a**−**d** cannot be formed from free ligands and titanium tetraisopropoxide. We therefore focused our attention on the involvement of the diethylzinc in the initial reaction with the ligand. It has been established that dialkylzinc reagents react with the bis(sulfonamide) ligands of the type **1a**−**d**.[31−37] Denmark[38] has recently shown that diethylzinc reacts with bis(sulfonamide) ligands to generate bis(sulfonamido) zinc species. We examined the reverse addition in the asymmetric alkylation, wherein the diethylzinc and the ligands **1a**−**c** were combined at 23 °C. On addition of diethylzinc to a solution of the ligand in toluene, a gas (ethane) was evolved. After cooling to −78 °C, a hexane solution of titanium tetraisopropoxide was added followed by the benzaldehyde. The reaction mixture was placed in the −25 °C bath. The ee's of the resulting 1-phenyl-1-propanol produced using **1a**−**c** were 98, 93, and 83%, respectively. These results indicate that the catalyst can be generated from the bis(sulfonamido) zinc complexes.

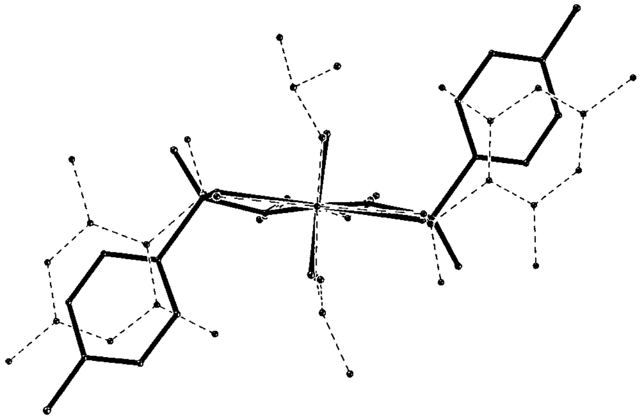

Figure 2. Overlay of **2a** and **2d**. The carbons of the isopropoxy groups of **2a** have been removed for clarity.

To explore the possibility of aggregation of the catalyst under the reaction conditions, we systematically varied the enantiopurity of the ligand **1a** and determined the ee's of the 1-phenyl-1-propanol produced. Monomeric catalysts generate product which exhibit a linear relationship between the ee of the catalyst and the ee of the product.[39] This was found to be the case with the bis(sulfonamide)/titanium system and indicates that the catalytically active species is monomeric.

To better understand the factors which control the enantioselectivity in this ligand accelerated addition,[40] we have examined the structure/enantioselectivity relationship between **2a** and **2d**. An overlay of the structures **2a** and **2d** was performed by superimposing the cyclohexyl rings, the sulfonamide nitrogens and the titanium centers (Figure 2). Although the solid-state structures are similar, the differences in the geometries are easily seen. The mesityl groups of **2d** are positioned further away from the titanium center than the tolyl groups in **2a**. This deviation is due to the increased steric hindrance of the ortho methyl substituents of **2d**. This difference in ground-state geometries of **2a** and **2d** will be amplified in the more sterically congested transition state and may be responsible for the large differences in the ee's of these catalysts (96% ee for **2a**, 19% ee for **2d**).

The results presented here, in conjunction with those of Ohno[12−14] and Knochel,[41] allow several conclusions about the mechanism of the reaction to be drawn. It has been shown by Ohno that the addition reaction with the bis(sulfonamide) ligands does not readily proceed in the absence of titanium tetraisopropoxide or in the presence of other metals. Knochel has found that the enantioselectivities are dependent on the nature of the titanium alkoxide used [$Ti(OR)_4$, R = *i*-Pr, *t*-Bu]. Taken together with our work, these results suggest that the bis(sulfonamide) ligands are bound to titanium in the active catalytic species.

We are continuing the investigation of the mechanism of this process as well as developing new catalysts derived from the bis(sulfonamide) ligands.[42]

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Supporting Information Available: The characterization and X-ray crystal structure data for **2a**−**d** (27 pages, print/PDF). See any current masthead page for ordering and Web access instructions.

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