Structural and Electronic Effects in Asymmetric Diethylzinc Addition to Benzaldehyde Catalyzed by Titanium(IV) Complexes of *N*-Sulfonylated *β*-Amino Alcohols

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A series of *N*-sulfonylated *β*-amino alcohols (*R,S*)-**3**, (1*R*,2*S*)-PhCH(OH)CH(NHSO$_2$R)CH$_2$Ph, was prepared from reaction of various alkyl- or aryl-sulfonyl chlorides with (1*R*,2*S*)-2-amino-1,3-diphenylpropanol. A ^{1}H NMR study of these ligands shows a correlation of electron-withdrawing abilities of ligands with electronic properties of R substituents on the sulfonyl group. The asymmetric diethylzinc additions to benzaldehyde catalyzed by titanium(IV) complexes of (*R,S*)-**3** were carried out, and yields and enantioselectivities of the desired (*R*)-1-phenylpropanol increase with increasing electron-donating abilities of R substituents. A dimeric titanium(IV) complex **4** was prepared, and the structure of **4** shows an interesting feature of inequivalent titanium metal centers with one sulfonamide of the chiral ligand bonded to a Ti metal center in a η^2-fashion and another sulfonamide bonded to the second Ti metal center in a η^1-fashion. The complex **4** is not an effective catalyst for the asymmetric diethylzinc addition reaction. With further addition of Ti(O-*i*-Pr)$_4$, the resulting systems become effective with results nearly identical to the in situ-formed catalytic systems. Another interesting feature is that the ^{1}H spectrum of **4** shows the presence of at least four isomeric species in CD$_2$Cl$_2$ at 0 °C, and possible structures of these species are discussed.

Introduction

The asymmetric diethylzinc addition to aldehydes has attracted considerable attention in the past decade since it is one of the most reliable reactions for testing the effectiveness of newly developed chiral ligands.[1] In the studies, C_2-symmetric chiral diols,[2] BINOLs,[3] and disulfonamides[4] were shown to be excellent ligands for the reactions. Recently, C_1-symmetric ligands such as derivatives of *β*-amino alcohols[5] and others[6] were developed and also demonstrated as excellent ligands. For asymmetric diethylzinc additions to aldehydes catalyzed by titanium(IV) complexes, the active catalytic systems were, in general, generated in situ from mixing the chiral ligand with excess Ti(OR)$_4$. To explore the role of excess Ti(OR)$_4$ and to elucidate the possible active species in catalytic systems, an increasing number of chiral titanium(IV) complexes have been prepared in the past 5 years and their structures were determined.[7] In several cases, chiral titanium(IV) complexes of known

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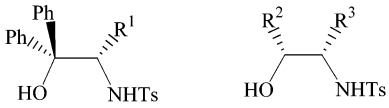
structures were examined as possible catalysts, and without the addition of $Ti(OR)_4$, they were proven to be ineffective in asymmetric diethylzinc addition reactions.[7d,8] Apparently, excess $Ti(OR)_4$ plays an important role in the reactions. The role of excess $Ti(OR)_4$ had been suggested to facilitate the removal of chiral products from the titanium metal center,[9] to exchange an ethyl group from diethylzinc for an alkoxide group of $Ti(OR)_4$ followed by transferring the ethyl to aldehyde attached to the chiral titanium center,[10] or to afford an effective species which is probably a dinuclear species with a Ti/chiral ligand ratio of 2:1 in solution.[8] However, further studies are required to provide evidence for the detailed mechanistic aspects of the reaction.

We have previously reported the synthesis of a series of *N*-sulfonylated *β*-amino alcohols (*S*)-**1** with only one stereogenic center and (*R*,*S*)-**2** with two stereogenic centers.[11] Asymmetric diethylzinc additions to aldehydes were examined employing titanium(IV) complexes of (*S*)-**1** or (*R*,*S*)-**2**, and the results show that ligands with two stereogenic centers, (*R*,*S*)-**2**, are in general better ligands than (*S*)-**1**.[11c] For (*R*,*S*)-**2** ligands, R^2 with aromatic groups such as in (*R*,*S*)-**2a**,**b**,**e** exhibit much better enantioselectivities than R^2 with aliphatic substituents such as in (*R*,*S*)-**2c**,**d**. For R^2 with aromatic groups, **2a** with the benzyl R^3 substituent is proven to have higher enantioselectivities than **2e** with the phenyl substituent. The best ligand is (*R*,*S*)-**2a** with 100% yield of the desired secondary alcohol and 96% ee of *R*-configuration. We report here the synthesis of a series of *N*-sulfonylated *β*-amino alcohols (*R*,*S*)-**3** with variations of sulfonyl R groups that are aliphatic or aromatic substituents. Structural and electronic effects of these ligands in asymmetric diethylzinc additions to benzaldehyde were examined, and the results show that R groups with an aromatic substituent give higher enantioselectivities than R groups with an aliphatic substituent. Electronically, R groups with an electron-donating substituent are better in stereocontrol than R with an electron-withdrawing substituent. In this study, a dimeric titanium(IV) complex of ligand (*R*,*S*)-**3d** was prepared and its structure was determined. This dimeric complex is shown to be ineffective as a catalyst. However, the same enantioselectivity as the in situ-formed system can be achieved with the addition of $Ti(O\text{-}i\text{-}Pr)_4$ to the dimeric complex.

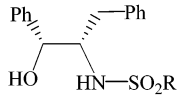
Results and Discussion

Synthesis and ^{1}H NMR Spectroscopic Characterization of (*R*,*S*)-3. To explore structural and electronic effects of substituents on the *N*-sulfonyl group, a series of *N*-sulfonylated *β*-amino alcohols *(R*,*S*)-**3** is prepared in 69% to quantitative yield from reactions of various alkyl- or aryl-sulfonyl chlorides with the (1*R*,2*S*)-1,3-diphenyl-2-aminopropanol in the presence of triethylamine and a catalytic amount of DMAP (4-*N*,*N*-(dimethylamino)pyridine). In this study, R groups with aliphatic substituents such as in **3a**,**b** and R groups with aromatic substituents such as in **3c**−**h** are included for elucidation of structural effects in asymmetric alkylation reactions. In each category of ligands, R with electron-donating groups such as in ligands **3a** (R = CH_3), **3c** (R = *p*-$CH_3OC_6H_4$), and **3d** (R = *p*-$CH_3C_6H_4$) or with electron-withdrawing substituents such as in ligands **3b** (R = CF_3) and **3f**−**h** (R = *p*-$CF_3C_6H_4$, *p*-$NO_2C_6H_4$, C_6F_5) are subjected to a study of the electronic effect.



1a: $R^1 = CH_3$
1b: R^1 = Ph
1c: $R^1 = PhCH_2$

2a: R^2 = Ph, $R^3 = PhCH_2$
2b: R^2 = *p*-$CH_3C_6H_4$, $R^3 = PhCH_2$
2c: R^2 = cyclohexyl, $R^3 = PhCH_2$
2d: R^2 = *t*-Bu, $R^3 = PhCH_2$
2e: $R^2 = R^3$ = Ph



3a: R = CH_3
3b: R = CF_3
3c: R = *p*-$CH_3OC_6H_4$
3d: R = *p*-$CH_3C_6H_4$ (= **2a**)
3e: R = C_6H_4
3f: R = *p*-$CF_3C_6H_4$
3g: R = *p*-$NO_2C_6H_4$
3h: R = C_6F_5

The *N*-sulfonyl group is an electron-withdrawing substituent, and for studying relative electron-withdrawing abilities of ligands, ^{1}H NMR spectroscopy is a good probe for this purpose. For example, an electron-withdrawing R substituent is expected to enhance the electron-withdrawing ability of the *N*-sulfonyl group and thus to decrease shielding of neighboring protons, which makes resonances of these protons, especially N*H* and NC*H* protons, appear relatively downfield. In contrast, an electron-donating R substituent would reduce the electron-withdrawing ability of the *N*-sulfonyl group and thus make neighboring protons to the *N*-sulfonyl group to appear comparably upfield. The selected ^{1}H chemical shifts of N*H* and NC*H* groups of (*R*,*S*)-**3** are listed in Table 1. It shows that the N*H* and NC*H* resonances appear downfield for R with electon-withdrawing CF_3 (**3b**) relative to the chemical shifts for the electron-donating CH_3 substituent (**3a**) by 0.45 and 0.18 ppm, respectively. For aromatic R substituents, a similar trend is observed with the relative electron-donating abilities in the order of *p*-$CH_3OC_6H_4$ (**3c**) > *p*-$CH_3C_6H_4$ (**3d**) > C_6H_5 (**3e**). For electron-withdrawing aromatic R substituents, a relative order of R = C_6F_5 (**3h**) > *p*-$NO_2C_6H_4$ (**3g**) > *p*-$CF_3C_6H_4$ (**3f**) is observed.

Asymmetric $ZnEt_2$ Addition to Benzaldehyde Catalyzed by Titanium(IV) Complexes of (*R*,*S*)-3. We have previously reported the asymmetric diethylzinc additions to aldehydes using titanium(IV) complexes of (*R*,*S*)-**2** ligands containing different R^2 and R^3 attached to the two chiral carbons. For benzaldehyde as a

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Table 1. Selected ^{1}H NMR Spectra of (*R*,*S*)-3[a]

chiral ligand	R	N*H*	NC*H*
3a	CH_3	4.647	3.802
3b	CF_3	5.103	3.978
3c	*p*-$CH_3OC_6H_4$	4.561	3.606
3d	*p*-$CH_3C_6H_4$	4.567	3.637
3e	*p*-C_6H_5	4.617	3.657
3f	*p*-$CF_3C_6H_4$	4.844	3.669
3g	*p*-$NO_2C_6H_4$	4.902	3.715
3h	C_6F_5	5.373	3.973

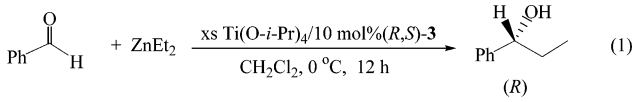
[a] 400 MHz in $CDCl_3$. Chemical shifts in ppm.

Table 2. Asymmetric Diethylzinc Additions to Benzaldehyde Catalyzed by in Situ-Formed Titanium(IV) Complexes of (*R*,*S*)-3[a–c]

			Ti(O-*i*-Pr)$_4$/L*					
			5		10		15	
entry	ligand (mol %)	R	yield	ee	yield	ee	yield	ee
1	**3a** (10)	CH_3	82.5	35.2	97.8	71.2	100	82.7
2	**3b** (10)	CF_3	72.7	64.9	90.0	73.2	97.7	66.8
3	**3c** (10)	*p*-$CH_3OC_6H_4$	86.0	86.4	99.0	95.3	100	96.2
4	**3d** (10)[d]	*p*-$CH_3C_6H_4$			100	96		
5	**3e** (10)	C_6H_5	45.0	68.0	83.0	93.0	93.0	94.0
6	**3f** (10)	*p*-$CF_3C_6H_4$	78.0	82.0	90.0	94.0	92.0	95.0
7	**3g** (10)	*p*-$NO_2C_6H_4$	66.5	75.6	90.3	89.0	93.0	91.9
8	**3h** (10)	C_6F_5	84.7	43.9	96.1	79.1	99.3	81.4

[a] Reaction conditions: chiral ligand L*, 0.05 mmol (10 mol %); $ZnEt_2$ (1.0 M in C_6H_{14}), 0.75 mmol; benzaldehyde, 0.5 mmol; solvent, CH_2Cl_2; reaction time, 12 h. [b] Yields (%) were determined by ^{1}H NMR. [c] ee (%) values were determined by HPLC using a Chiralcel OD column from Daicel. [d] Taken from ref 11c.

substrate and (*R*,*S*)-**2a** with R^2 = Ph and R^3 = CH_2Ph as a ligand in a catalytic system with a Ti(O-*i*-Pr)$_4$/(*R*,*S*)-**2a** ratio of 10:1, the reaction gives a 100% yield of the desired (*R*)-1-phenylpropanol with an outstanding 96% ee. For ligands (*R*,*S*)-**3** with the same R^2 = Ph and R^3 = CH_2Ph, but with variations of R substituents at the sulfonyl group, asymmetric addition reactions to benzaldehyde were carried out under the same reaction conditions (eq 1), and the results are listed in Table 2.

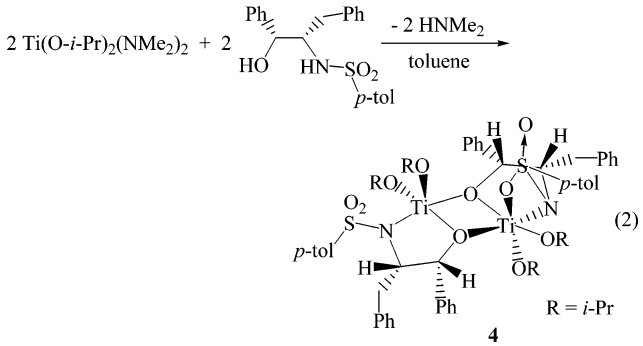


(1)

The catalytic systems were generated in situ from mixing excess Ti(O-*i*-Pr)$_4$ with a (*R*,*S*)-**3** ligand (denoted as L*) at Ti(O-*i*-Pr)$_4$/L* ratios of 5, 10, and 15. From the table, a general feature of increasing both yields and enantioselectivities with increasing the Ti/L* ratios is observed except for the case of ligand **3b**. For **3b**, the yield increases from a system at the Ti/L* ratio of 5 of 72.7% to a system of the ratio at 15 of 97.7% (entry 1). However, the ee value reaches a maximum 73.2% at the Ti/L* ratio of 10 and then decreases to 66.8% while increasing the Ti/L* ratio to 15 (entry 2). For ligands **3c** and **3e**−**h**, ee values reach to nearly maximum at the Ti/L* ratio of 10 (entries 3, 5−8). In terms of structural differences of ligands **3**, aliphatic R groups of CH_3 and CF_3 in the catalytic system at the Ti/L* ratio of 10 give lower enantioselectivities of 71.2% ee (entry 1) and 73.2% ee (entry 2), respectively. However, ligands with the aromatic R substituent give much higher enantiocontrol at 89% ee or above, except for ligand **3h**, with 79.1% ee (entry 8). These results show a superior structural effect of aromatic R substituents relative to aliphatic R substiuents of CH_3 and CF_3. For ligands **3c**−**h**, the enantioselectivity obtained from the catalytic system at the Ti/L* ratio of 10 decreases from 95.3% for **3c** (R = *p*-$CH_3OC_6H_4$) (entry 3) and 96% for **3d** (R = *p*-$CH_3C_6H_4$) (entry 4) to 79.1% for **3h** (R = C_6F_5) (entry 8). The observed trend is parallel to increasing electron-withdrawing abilities from **3c** to **3h** (cf. Table 1). Similar results are observed for aliphatic R substituents in the catalytic system at the Ti/L* ratio of 15 with **3a** (R = CH_3), giving a higher ee value of 82.7% than **3b** (R = CF_3) of 66.8%. The above results exhibit that an increase of the electron-donating ability of the aromatic R group enhances the stereocontrol of the desired product and the electronic effect is increased by 20% ee from the most electron-withdrawing **3h** ligand to ligands **3c** and **3d** with the electron-donating R substituent. Apparently, the R substituent fine-tunes the electronic state of the titanium metal center, and a better electron-donating R group reduces the electron-withdrawing ability of the sulfonamide nitrogen donor, affording a catalytic system for better stereocontrol.

The study of nonlinear effect was conducted on the best performing ligand, **3d**, and the results are shown in Figure 1. Yields for the secondary alcohol range from 86 to 100% for ligand **3d** of different ee values, and it is found that enantioselectivities are independent from yields of the product. The observed small negative nonlinear effect suggests that the active species contains only one *N*-sulfonylated *β*-amino alcoholate ligand and that the two enantiomeric active species have similar reactivities in the asymmetric diethylzinc addition reaction.

Synthesis and Molecular Structure of the Dimeric Titanium(IV) Complex 4. To explore the structure of titanium(IV) complexes of chiral ligands, a reaction of Ti(O-*i*-Pr)$_2$(NMe$_2$)$_2$ with 1 molar equiv of (*R*,*S*)-**3d** in toluene was carried out, and complex **4** is obtained in 58.7% yield as orange crystals from a solution of toluene/hexane (eq 2).



(2)

Complex **4** crystallizes in the triclinic *P*1 space group, and the crystal structure shows that each unit cell contains two independent dimeric complex **4** molecules and a solvated toluene molecule. Structural data for both molecules are nearly identical, and the structure of only one molecule is shown in Figure 2. Selected bond lengths and bond angles for the structure shown in Figure 2 are listed in Table 3. Complex **4** is a dimeric titanium(IV) species with two metal centers bridged by the alkoxy donor of the chiral ligand. The most interesting feature of the structure is inequivalence of two

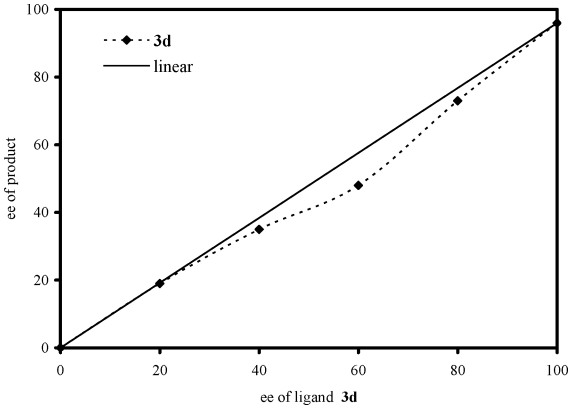


Figure 1. Nonlinear effect of the **3d**/Ti(O-*i*-Pr)$_4$ catalytic system in asymmetric diethylzinc addition to benzaldehyde.

titanium metal centers due to different bonding modes of the sulfonamide of the two chiral ligands. One sulfonamide bonds to the Ti(1) metal in an η^2-fashion to make the metal center six-coordinated with a Ti(1)−N(1) distance of 2.069(5) Å and a Ti(1)−O(2) bond length of 2.486(5) Å. Another sulfonamide bonds to the Ti(2) in an η^1-fashion to give a five-coordinate Ti metal center with a slightly longer Ti(2)−N(31) distance of 2.105(6) Å. The nonbonded Ti(2)···O(33) distance is much longer at 3.056 Å. For the six-coordinate Ti(1) moiety, Ti(1)−O(*i*-Pr) distances are longer at 1.787(6) and 1.760(5) Å than the distances of 1.721(6) and 1.745(5) Å for the five-coordinate Ti(2) metal moiety. In the six-coordinate Ti(1) moiety, the bridging alkoxy O(1) and the 2-propoxy O(5) occupy axial positions with an O(1)−Ti(1)−O(5) angle of 165.6(2)°. Two Ti(1)−O−C angles of 2-propoxide ligands are close to linear at 164.0(12)° and 162.2(8)°, indicating a good π-donor of alkoxide ligands. The five-coordinate Ti(2) moiety has a distorted trigonal bipyramidal geometry, and the bridging O(1) and the amide N(31) donor occupy axial positions with an O(1)−Ti(2)−N(31) angle of 146.0(2)°. This small axial angle is due to a structural restraint of the chiral ligand in a bridging bidentate bonding fashion. The two Ti(2)−O−C angles of 2-propoxide ligands are also close to linear at 167.6(9)° and 154.7(6)°.

Table 3. Selected Bond Lengths (Å) and Bond Angles (deg) for Complex 4

Bond Lengths			
Ti(1)−O(1)	2.079(4)	Ti(2)−O(1)	2.025(4)
Ti(1)−O(2)	2.486(5)	Ti(2)···O(33)	3.056
Ti(1)−O(4)	1.787(6)	Ti(2)−O(34)	1.721(6)
Ti(1)−O(5)	1.760(5)	Ti(2)−O(35)	1.745(5)
Ti(1)−N(1)	2.069(5)	Ti(2)−N(31)	2.105(6)
Ti(1)−O(31)	1.961(4)	Ti(2)−O(31)	2.031(4)
S(1)−O(2)	1.441(5)	S(31)−O(32)	1.439(6)
S(1)−O(3)	1.433(5)	S(31)−O(33)	1.447(6)
S(1)−N(1)	1.583(6)	S(31)−N(31)	1.597(6)
Ti(1)···Ti(2)	3.266(2)		
Bond Angles			
O(1)−Ti(1)−O(5)	165.6(2)	O(1)−Ti(2)−N(31)	146.0(2)
O(2)−Ti(1)−N(1)	62.6(2)	O(31)−Ti(2)−O(34)	121.9(2)
O(4)−Ti(1)−O(31)	104.1(2)	O(31)−Ti(2)−O(35)	126.0(2)
O(1)−Ti(1)−O(31)	71.5(2)	O(34)−Ti(2)−O(35)	111.8(3)
Ti(1)−O(4)−C(23)	164.0(12)	Ti(2)−O(34)−C(53)	167.6(9)
Ti(1)−O(5)−C(26)	162.2(8)	Ti(2)−O(35)−C(56)	154.7(6)
O(2)−S(1)−O(3)	116.8(4)	O(32)−S(31)−O(33)	118.8(4)
O(2)−S(1)−N(1)	104.4(3)	O(32)−S(31)−N(31)	112.8(4)
O(3)−S(1)−N(1)	114.2(3)	O(33)−S(31)−N(31)	106.3(3)

A closely related dimeric titanium(IV) complex **6** prepared from the chiral sulfonamide alcohol **5** was reported by Gagné et al.[7c] Unlike the structure of **4**, both sulfonamide groups in **6** bond to two Ti metal centers in an η^1-fashion, giving both metal centers of five coordinations. The average Ti−O(μ) bond distance of **6** at 2.029 Å is similar to the distance of 2.024 Å for the complex **4**. The average Ti−O(*i*-Pr) distance of 1.741 Å is slightly longer than the average distance of 1.733 Å in the five-coordinate metal moiety in **4**. But the distance is shorter by 0.019 and 0.046 Å than the bond lengths in the six-coordinate titanium moiety. The average Ti−N bond length of 2.0896 Å is slightly longer than the Ti−N distance of 2.069 Å in the six-coordinate metal moiety in complex **4**, but slightly shorter than the five-coordinate Ti−N bond distance of 2.105 Å. The differences for the chiral ligand **5** with **3d** are that the ligand **5** contains an electron-withdrawing sulfonyl CF_3

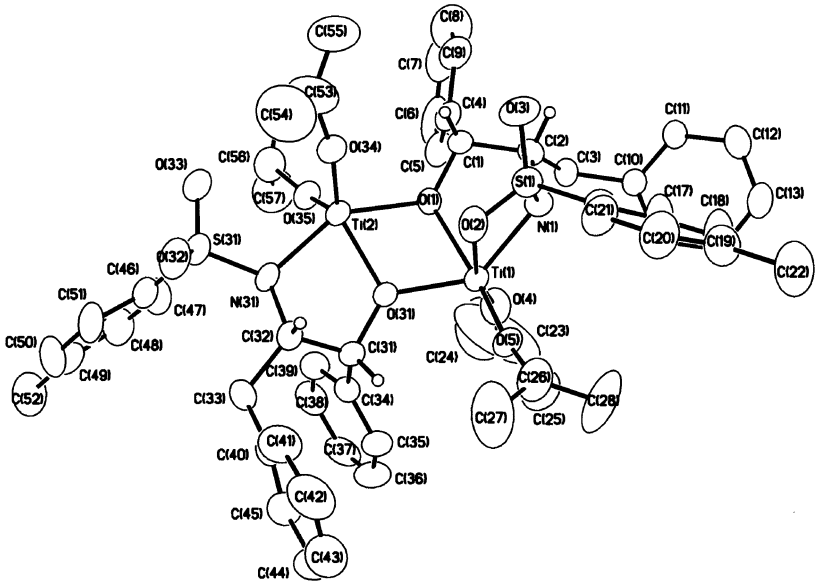
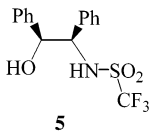


Figure 2. Molecular structure of complex **4**. Hydrogen atoms, except those attached to chiral carbons, are omitted for clarity.

substituent and a phenyl group at the amide chiral carbon instead of an electron-donating sulfonyl *p*-tolyl group and a benzyl substituent at the amide chiral carbon in **3d**.



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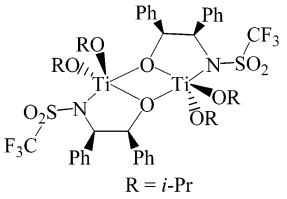
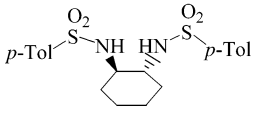


R = *i*-Pr

6



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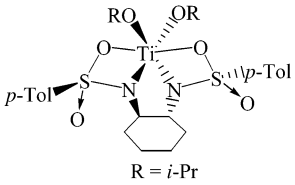


R = *i*-Pr

8

For the disulfonamide ligand **7** containing the same sulfonyl *p*-tolyl substituent, a monomeric titanium(IV)-disulfonamide complex **8** was prepared by Walsh et al.[7a] Both sulfonamides bond to the metal center in an η^2-fashion to give the monomeric six-coordinate structure **8**. Compared to the structure of **4**, the average Ti−O(*i*-Pr) distance of 1.768 Å in **8** is comparable to 1.774 Å for Ti−O(*i*-Pr) bonds in the six-coordinate titanium moiety in **4**, but is longer by 0.035 Å than the distance in the five-coordinate metal moiety. The average Ti−O(sulfonyl) bond length at 2.309 Å is much shorter than the distance of 2.486(5) Å in **4**, and the average Ti−N distance of 2.054 Å in **8** is also shorter than the distances of 2.069(5) and 2.105(6) Å in **4**. The long Ti−O(sulfonyl) bond in **4** may be due to structural differences of the six-coordinate Ti(1) moiety in **4** from the structure **8**. Since the Ti−O(sulfonyl) bond in **4** is relatively weak, there is another possibility that this interaction is due to an effect of crystal packing.[12]

From structures **4** and **8**, the sulfonamide group bearing the electron-donating *p*-tolyl substituent shows a feature of the η^2-bonding in contrast to the η^1-bonding for the sulfonamide bearing the electron-withdrawing CF_3 substituent. Both **3d**/Ti(O-*i*-Pr)$_4$ and **7**/Ti(O-*i*-Pr)$_4$ systems are effective catalysts for the asymmetric diethylzinc additions to aldehydes. The ligand **5** is structurally more related to the **3b** (R = CF_3) ligand, and from the result of 90.0% yield and 73.2% ee employing the **3b**/Ti(O-*i*-Pr)$_4$ catalytic system (Table 1, entry 2), the **5**/Ti(O-*i*-Pr)$_4$ system may not be as good a catalytic system as the **3d**/Ti(O-*i*-Pr)$_4$ or the **7**/Ti(O-*i*-Pr)$_4$ system. Does the η^2-bonding of the sulfonamide donor provide a suitable environment around the metal center for achieving higher stereocontrol? At this moment, it is not clear if the η^2-sulfonamide bonding plays an important role in the asymmetric diethylzinc addition reaction.

Asymmetric Diethylzinc Addition to Benzaldehyde Using 4/Ti(O-*i*-Pr)$_4$ Catalytic Systems. Complex **4** as a possible catalyst for the asymmetric diethylzinc addition to benzaldehyde was examined, and the results are listed in Table 4. Under the same reaction conditions as described in Table 2, the reaction employing 0.025 mmol of complex **4** (10 mol % loading in (*R*,*S*)-**3d**) as a catalyst gives the desired product in only 9.2% yield (entry 1), and there is no attempt to purify the product for ee value determination. Apparently, only complex **4** is not an effective catalyst for the reaction. However, with the addition of 0.15 mmol of Ti(O-*i*-Pr)$_4$ to the solution of 5 mol % **4**, giving a system with a Ti/L* ratio of 4, both yield and enantioselectivity increase remarkably to 80.7% and 86.7% ee (entry 2), respectively. When the Ti/L* ratio further increases to 8, the reaction gives a maximum yield of 100% and the enantioselectivity also reaches a maximum 96.3% ee (entry 3). Further increasing the Ti/L* ratio to 10 affords nearly the same yield of 99.0% and a comparable ee value of 95.5% (entry 4). The above result is nearly identical to the values from the in situ-formed catalytic system with the same Ti/L* ratio of 10 (Table 2, entry 4). As long as the Ti/L* ratios are kept the same, it seems that the same effective catalytic species is generated either from mixing complex **4** or from mixing the chiral ligand (*R*,*S*)-**3d** with an appropriate amount of Ti(O-*i*-Pr)$_4$.

Table 4. Asymmetric Diethylzinc Addition to Benzaldehyde Catalyzed by the Complex 4/Ti(O-*i*-Pr)$_4$ System[a−c]

entry	complex **4** (mmol)	Ti(O-*i*-Pr)$_4$ (mmol)	Ti/L* ratio	yield (%)	ee (%)
1	0.025	0	1	9.2	
2	0.025	0.15	4	80.7	86.7
3	0.025	0.35	8	100	96.3
4	0.025	0.45	10	99.0	95.5

[a] Reaction conditions: $ZnEt_2$, 0.75 mmol (1.0 M in C_6H_{14}); benzaldehyde, 0.5 mmol; solvent, CH_2Cl_2; reaction time, 12 h; reaction temperature, 0 °C. [b] Yields (%) were determined by ^{1}H NMR. [c] ee (%) values were determined by HPLC using a Chiralcel OD column from Daicel.

^{1}H NMR Spectroscopic Study of Complex 4/Ti(O-*i*-Pr)$_4$ Systems. For demonstrating the presence of the common effective catalytic species in solution, ^{1}H NMR study of complex **4** without and with the addition of Ti(O-*i*-Pr)$_4$ was conducted and the selected ^{1}H NMR spectra in the PhC*H*(O−)− region are shown in Figure 3. Figure 3(a) shows a spectrum of complex **4**, and on the basis of the unsymmetric dimeric solid state structure of **4**, two equivalent sets of ^{1}H NMR resonances are expected if the solid structure of **4** remains intact in solution. However, a complicated spectrum is observed in CD_2Cl_2 and a careful examination of the spectrum suggests the presence of at least four species in CD_2Cl_2 for the same sample as that for the X-ray structural determination. For structural elucidations of **4** in solution, some possible dimeric isomers are shown in Figure 4. Each symmetric structure **4b**, **4c**, or **4f** would give rise one doublet of C*H* resonance and each unsymmetric structure **4a**, **4d**, or **4e** would give two equivalent doublets. The major doublet at δ 5.634 ppm with a relative intensity of 58.8% is likely due to the resonance of the symmetric structure **4b** with both sulfonamides bonded to Ti metal centers in η^1-fashion or structure **4c** with both sulfonamides bonded in η^2-fashion. Entropically, structure **4b** is more favored in solution. The set of two equivalent doublets at δ 5.694 and 5.064 ppm with a combined intensity of 26.2% is

(12) Pritchett, S.; Gantzel, P.; Walsh, P. J. *Organometallics* **1997**, *18*, 55130.

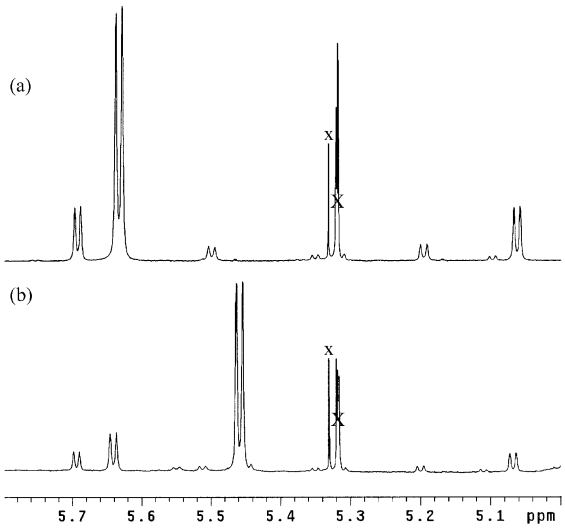


Figure 3. Selected ^{1}H NMR spectra in the region of PhC*H*(O−)− at 600 MHz in CD_2Cl_2 at 0 °C: (a) complex **4** and (b) complex **4** + 18 equiv of Ti(O-*i*-Pr)$_4$ (Ti/L* = 10:1). x: impurity; X: solvent.

apparently due to structure **4a**, which is the structure in the solid state. Another set of two equivalent doublets at δ 5.500 and 5.196 ppm accounting for 11.7% abundance is likely due to the C*H* resonances of the structure **4d**, which is expected to be higher in energy due to moving one 2-propoxide ligand into the bridging position. Of the minor resonances, a set of equivalaent doublets at δ 5.351 and 5.098 ppm with 6.4% intensity is likely due to the unsymmetric structure **4e**.

Since the best enantioselectivity is achieved with a catalytic system having the Ti/L* ratio of 10, the spectrum of complex **4** with the addition of 18 equiv of Ti(O-*i*-Pr)$_4$, which gives a system of also Ti/L* = 10, is shown in Figure 3(b). In addition to resonances for complex **4**, two new species are observed with *CH* resonances appearing at δ 5.459 ppm as a doublet of 49.4% abundance and at δ 5.550 and 5.447 ppm as one set of two equivalent doublets of ∼9.00%. In contrast, abundances for the species of the complex **4** decrease to 13.9% (**4b**), 15.9% (**4a**), 8.5% (**4d**), and 6.3% (**4e**). Since complex **4** is demonstrated to be ineffective for the reaction, the major new species with a *CH* doublet at δ 5.459 is considered to be the effective species in solution.

Comment on the Role of Excess Ti(O-*i*-Pr)$_4$ in the Catalytic System. It is a general feature that excess Ti(O-*i*-Pr)$_4$ is required in order to achieve high enantioselectivities for asymmetric diethylzinc additions to aldehydes catalyzed by titanium(IV) complexes of chiral bidentate ligands. For chiral diols derived from D-mannitol, a dimeric titanium complex **9** bridged by the chiral diolates[8] was prepared, and the dimeric species **9** is not an effective catalyst for the asymmetric addition reaction with a yield of only 16% and an enantioselectivity of 50% ee. However, with the addition of Ti(O-*i*-Pr)$_4$ to the complex to make the catalytic system with a Ti/L* ratio of 10, both yield and enantioselectivity improve dramatically to 100% and 85% ee, respectively. In that study, it was shown that the added Ti(O-*i*-Pr)$_4$ reacts with the dimeric complex **9** to afford a new dimeric complex **10**, which is in equilibrium with the complex **9** in solution. The amount of **10** increases with increasing addition of Ti(O-*i*-Pr)$_4$, and enantioselectivities also increase in the same manner. Although complex **10** could not be isolated, the presence of **10** is suggested both from the ^{1}H NMR study and from the FAB-mass spectroscopy. For the BINOL ligand, a dimeric Ti(IV) complex **11** prepared from the racemic BINOL was reported in an elaborated work by Walsh et al.[10] Complex **11** is a dimeric species that closely resembles structure **10**. They suggest that the chiral complex **11** is an active species in the catalytic system and that diethylzinc does not transfer an ethyl group directly to the aldehyde attached to the chiral titanium center. Instead, the diethylzinc transfers an ethyl group to one of the titanium metal centers in the complex **11** and then to the attached aldehyde to give the desired product. Complex **4** was slow to catalyze the asymmetric reaction, and a higher Ti/L* ratio is required for achieving the best yield and enantioselectivity. The ^{1}H NMR study of complex **4**/Ti(O-*i*-Pr)$_4$ systems shows that complex **4** reacts with excess Ti(O-*i*-Pr)$_4$ giving a new species of ∼50% abundance, which is likely the effective species in the catalytic reaction. Although the structure of this new species in not clear at this moment, the new species may have a structure similar to **10** or **11** based on the observations of (1) the same feature of excess Ti(O-*i*-Pr)$_4$ required for achieving the best enantioselectivity and (2) a new species generated from reaction of complex **4** with excess Ti(O-*i*-Pr)$_4$. The formation of

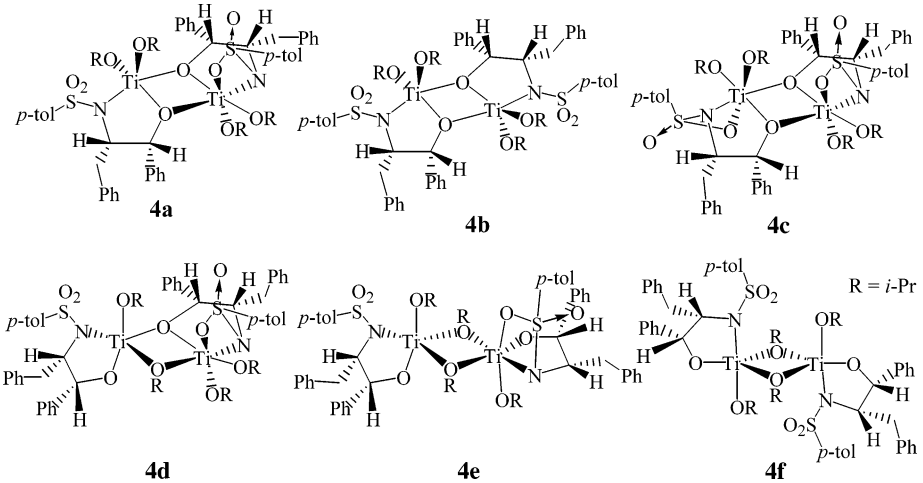
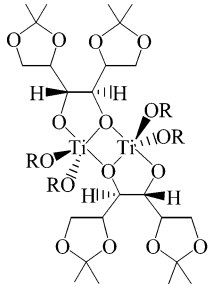


Figure 4. Possible isomeric structures of complex **4**.

the new dimeric active species with a Ti/L* ratio of 2:1 is suggested from the previous study of the derivative of the D-mannitol/Ti(O-*i*-Pr)$_4$ system.



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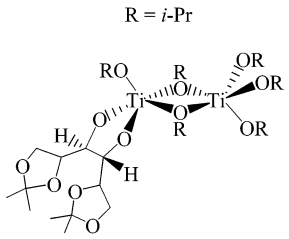

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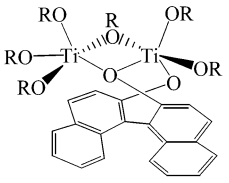

11

Conclusions

A series of *N*-sulfonylated *β*-amino alcohols (*R*,*S*)-**3** with variations of sulfonyl R groups was prepared, and the asymmetric diethylzinc addition reaction to benzaldehyde catalyzed by titanium(IV) complexes of (*R*,*S*)-**3** is demonstrated, affording excellent yields and enantioselectivities. It seems that the variations of R substituents on the sulfonyl group fine-tunes the catalytic system, with the best result obtained for ligands with R of electron-donating *p*-$CH_3OC_6H_4$ or *p*-$CH_3C_6H_4$. A dimeric titanium(IV) complex **4** was prepared, and the structure was determined. Although complex **4** alone is not an active catalyst, the addition of extra Ti(O-*i*-Pr)$_4$ gives an effective catalytic system. The ^{1}H NMR spectrum of complex **4** shows at least four isomeric species present in solution, and with the addition of Ti(O-*i*-Pr)$_4$ to complex **4**, the ^{1}H NMR spectrum reveals a major new species generated in solution. This new species is suggested to have a structure similar to **10** or **11**, and the role of excess Ti(O-*i*-Pr)$_4$ is to react with complex **4** to form a substantial amount of the dimeric active species in solution. Further studies including attempts at the preparation of the dimeric titanium(IV) complex of (*R*,*S*)-**3d** with a structure similar to the structure **10** or **11** are currently underway.

Experimental Section

Reagent and General Techniques. (1*R*,2*S*)-2-Amino-1,3-diphenyl-1-propanol was prepared on the basis of modified procedures reported by Reetz et al.[13] (1*R*,2*S*)-2-(4-Methylbenzenesulfonylamino)-1,3-diphenyl-1-propanol, (*R*,*S*)-**3d**, was prepared according to the literature procedure.[11c] NEt_3 was distilled and stored over dried molecular sieves. 4-(Dimethylamino)pyridine (DMAP, Lancaster) and diethylzinc (1.0 M solution in hexane, Fluka) were used directly. Sulfonyl chlorides were purchased from Aldrich and were used without further purification. Ti(O-*i*-Pr)$_4$ was freshly distilled prior to use. Benzaldehyde was distilled before use. Solvents were dried by refluxing for at least 24 h over P_2O_5 (dichloromethane) or sodium/benzophenone (*n*-hexane or toluene) and were freshly distilled prior to use. All syntheses and manipulations were carried out under a dry dinitrogen atmosphere.

Physical Measurements. ^{1}H NMR spectra were obtained with a Varian Inova Unity-600 (600 MHz), a Varian Mercury-400 (400 MHz), or a Varian Gemini-200 (200 MHz) spectrometer, and ^{13}C NMR spectra were recorded with the Varian Mercury-400 (100.70 MHz) or the Varian Gemini-200 (50.289 MHz) spectrometer. ^{1}H and ^{13}C chemical shifts were measured relative to tetramethylsilane as the internal reference. Melting points were taken on a Büchi 535 instrument and are uncorrected. Elemental analyses were performed using a Heraeus CHN-O-RAPID instrument. Optical rotations were determined on a Perkin-Elmer 241 polarimeter.

General Procedures for Synthesis of Sulfonylamino Alcohols (*R*,*S*)-3. To a solution of (1*R*,2*S*)-2-amino-1,3-diphenyl-1-propanol (0.227 g, 1.00 mmol), NEt_3 (0.418 mL, 3.00 mmol), and DMAP (0.006 g, 0.05 mmol) in 10 mL of CH_2Cl_2 at 0 °C was added dropwise sulfonyl chloride (1.00 mmol) in 5 mL of CH_2Cl_2 with stirring. After the addition was complete, the solution was allowed to warm to room temperature and to react for 16 h. The reaction mixture was washed with 1 N HCl (10 mL), saturated $NaHCO_3$ (10 mL), and then saturated brine (10 mL), and the organic layer was dried over $MgSO_4$. The solution was filtered and dried under reduced pressure to give the desirerd *N*-sulfonated *β*-amino alcohol (*R*,*S*)-**3**.

(1*R*,2*S*)-2-(Methanesulfonylamino)-1,3-diphenyl-1-propanol, (1*R*,2*S*)-3a: white solid, 0.30 g (99.0%), mp 120−122 °C; $[\alpha]^{25}_D$ −38.44 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.12−7.46 (m, 10H, 2Ph), 5.01 (d, *J* = 3.2 Hz, 1H, PhC*H*OH), 4.64 (br, 1H, N*H*), 3.80 (m, 1H, C*H*N), 2.85 (br, 1H, O*H*), 2.77 (dd, *J* = 3.4, 13.6 Hz, 1H, PhCH_AH_B), 2.55 (dd, *J* = 10.8, 14.0 Hz, 1H, PhCH_AH_B), 2.11 (s, 3H, CH_3) ppm. ^{13}C{^{1}H} NMR (100.075 MHz, $CDCl_3$): *δ* 140.42, 138.38, 129.58, 128.49, 128.40, 127.66, 126.44, 126.08, 76.24, 62.58, 40.18, 34.42 ppm. Anal. Calcd for $C_{16}H_{19}NO_3S$: C, 62.93; H, 6.27; N, 4.59; O, 15.72. Found: C, 63.49; H, 6.32; N, 4.74; O, 15.51.

(1*R*,2*S*)-2-(Trifluoromethanesulfonylamino)-1,3-diphenyl-1-propanol, (1*R*,2*S*)-3b: white solid, 0.25 g (69.6%), mp 89−90 °C; $[\alpha]^{25}_D$ −10.64 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.07−7.46 (m, 10H, 2Ph), 5.10 (d, *J* = 8.0 Hz, 1H, N*H*), 5.03 (d, *J* = 3.2 Hz, 1H, PhC*H*OH), 3.98 (m, 1H, C*H*N), 2.77 (d, *J* = 7.2 Hz, 2H, PhCH_2) ppm. ^{13}C{^{1}H} NMR (100.075 MHz, $CDCl_3$): *δ* 139.36, 126.27, 129.40, 128.82, 128.61, 128.43, 126.98, 125.96, 75.72, 62.88, 34.55 ppm. Anal. Calcd for $C_{14}H_{16}NO_3F_3S$: C, 53.48; H, 4.49; N, 3.90. Found: C, 53.83; H, 4.65; N, 3.98.

(1*R*,2*S*)-2-(4-Methoxybenzenesulfonylamino)-1,3-diphenyl-1-propanol, (1*R*,2*S*)-3c: white solid, 0.36 g (90.6%), mp 48−50 °C; $[\alpha]^{25}_D$ −6.01 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 6.70−7.40 (m, 14H, 3Ph), 5.08 (d, *J* = 2.8 Hz, 1H, PhC*H*OH), 4.56 (d, *J* = 7.2 Hz, 1H, N*H*), 3.85 (s, 3H, CH_3), 3.61 (m, 1H, C*H*N), 2.93 (br, 1H, O*H*), 2.64 (dd, *J* = 4.2, 14.4 Hz, 1H, PhCH_AH_B), 2.50 (dd, *J* = 10.4, 14.4 Hz, 1H, PhCH_AH_B) ppm. ^{13}C{^{1}H} NMR (100.075 MHz, $CDCl_3$): *δ* 162.39, 140.31, 137.17, 130.86, 128.98, 128.81, 128.31, 128.27, 127.48, 126.17, 126.07, 113.94, 75.21, 61.23, 55.43, 33.99 ppm. Anal. Calcd for $C_{22}H_{23}NO_4S$: C, 66.48; H, 5.83; N, 3.52; O, 16.10. Found: C, 66.66; H, 5.97; N, 3.85; O, 16.33.

(1*R*,2*S*)-2-(Benzenesulfonylamino)-1,3-diphenyl-1-propanol, (1*R*,2*S*)-3e: white solid, 0.35 g (95.2%), mp 122−124 °C; $[\alpha]^{25}_D$ −26.41 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 6.80−7.47 (m, 15H, 3Ph), 5.08 (d, *J* = 3.2 Hz, 1H, PhC*H*OH), 4.62 (br, 1H, N*H*), 3.66 (m, 1H, C*H*N), 2.65 (dd, *J* = 4.0, 14.4 Hz, 1H, PhCH_AH_B), 2.53 (dd, *J* = 10.0, 14.4 Hz, 1H, PhCH_AH_B) ppm. ^{13}C{^{1}H} NMR (100.075 MHz, $CDCl_3$): *δ* 140.20, 139.39, 137.00, 132.14, 128.95, 28.79, 128.38, 128.36, 127.61, 126.68, 126.34, 75.26, 61.36, 33.99 ppm. Anal. Calcd for $C_{21}H_{21}NO_3S$: C, 68.64; H, 5.70; N, 3.81; O, 13.06. Found: C, 68.46; H, 5.73; N, 4.03; O, 13.23.

(13) Reetz, M. T.; Drewes, M. W.; Schmitz, A. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1141.

(1*R*,2*S*)-2-(4-Trifluoromethylbenzenesulfonylamino)-1,3-diphenyl-1-propanol, (1*R*,2*S*)-3f: white solid, 0.41 g (94.0%), mp 175−176 °C; $[\alpha]^{25}_D$ −47.64 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.76−7.49 (m, 14H, 3Ph), 5.12 (d, J = 3.2 Hz, 1H, PhC*H*OH), 4.84 (d, J = 7.2 Hz, 1H, N*H*), 3.67 (m, 1H, C*H*N), 2.79 (br, 1H, O*H*), 2.68 (dd, J = 3.4, 14.0 Hz, 1H, PhCH_AH_B), 2.52 (dd, J = 10.6, 14.4 Hz, 1H, PhCH_AH_B) ppm. ^{13}C{^{1}H} NMR (100.075 MHz, $CDCl_3$): δ 143.01, 140.09, 136.87, 133.44. 128.98, 128.59, 128.43, 127.96, 127.00, 126.63, 126.04, 125.91, 121.86, 75.81, 61.81, 34.25 ppm. Anal. Calcd for $C_{22}H_{20}NO_3F_3S$: C, 60.68; H, 4.63; N, 3.22. Found: C, 60.12; H, 4.78; N, 3.68.

(1*R*,2*S*)-2-(4-Nitrobenzenesulfonylamino)-1,3-diphenyl-1-propanol, (1*R*,2*S*)-3g: white solid, 0.33 g (80.0%), mp 173−174 °C; $[\alpha]^{25}_D$ −62.43 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.79−8.00 (m, 14H, 3Ph), 5.11 (d, J = 3.2 Hz, 1H, PhC*H*OH), 4.90 (d, J = 8.8 Hz, 1H, N*H*), 3.71 (m, 1H, C*H*N), 2.70 (dd, J = 3.6, 14.4 Hz, 1H, PhCH_AH_B), 2.55 (dd, J = 10.4, 14.4 Hz, 1H, PhCH_AH_B) ppm. ^{13}C{^{1}H} NMR (100.075 MHz, $CDCl_3$): δ 149.42, 145.45, 140.06, 137.13, 129.12, 128.65, 128.43, 128.03, 127.65, 126.50, 125.98, 123.92, 76.03, 62.16, 34.16 ppm. Anal. Calcd for $C_{21}H_{20}N_2O_5S$: C, 61.15; H, 4.89; N, 6.79; O, 19.40. Found: C, 61.34; H, 5.03; N, 6.80; O, 19.21.

(1*R*,2*S*)-2-(2,3,4,5,6-Pentafluorobenzenesulfonylamino)-1,3-diphenyl-1-propanol, (1*R*,2*S*)-3h: white solid, 0.36 g (79.0%), mp 146−148 °C; $[\alpha]^{25}_D$ −63.78 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.92−7.45 (m, 10H, 2Ph), 5.37 (d, J = 9.2 Hz, 1H, N*H*), 5.11 (d, J = 3.2 Hz, 1H, PhC*H*OH), 3.97 (m, 1H, C*H*N), 2.75 (dd, J = 3.4, 14.0 Hz, 1H, PhCH_AH_B), 2.59 (dd, J = 11.0, 14.0 Hz, 1H, PhCH_AH_B), 2.45 (br, 1H, O*H*) ppm. ^{13}C{^{1}H} NMR (100.075 MHz, $CDCl_3$): δ 145.02, 142.45, 140.10, 138.55, 137.33, 136.06, 128,92, 128.65, 128.11, 128.03, 126.39, 125.90, 76.47, 62.72, 33.92 ppm. Anal. Calcd for $C_{21}H_{16}NO_3F_5S$: C, 55.14; H, 3.53; N, 3.06. Found: C, 55.38; H, 3.71; N, 3.47.

Synthesis of Complex 4·1/2($C_6H_5CH_3$). (1*R*,2*S*)-2-(4-Methylbenzenesulfonylamino)-1,3-diphenyl-1-propanol (1.14 g, 2.00 mmol), Ti(O-*i*-Pr)$_4$ (0.426 g, 1.00 mmol), and Ti(NMe$_2$)$_4$ (0.336 g, 1.00 mmol) were mixed in 50 mL of toluene, and the resulting mixture was stirred at room temperature for 12 h. The solvent was removed under reduced pressure to give a yellow solid, which was recrystallized from toluene/hexane (3 mL/6 mL) at 4 °C to afford orange crystals (0.945 g, 58.7%), mp 96−98 °C. Anal. Calcd for ($C_{56}H_{70}N_2O_{10}S_2Ti_2$)·1/2($C_7H_8$): C, 62.85; H, 6.56; N, 2.46. Found: C, 62.44; H, 6.45; N, 2.63.

General Procedures for the Addition of Et_2Zn to Benzaldehyde Catalyzed by the (*R*,*S*)-3/Ti(O-*i*-Pr)$_4$ System. Under a dry dinitrogen atmosphere, the ligand (0.05 mmol) and Ti(O-*i*-Pr)$_4$ were mixed in 1.5 mL of dry dichloromethane at room temperature. After 1 h, 0.75 mmol of Et_2Zn (1.0 M solution in hexane) was added at 0 °C. After the mixture was stirred for 30 min, the light yellow solution was treated with benzaldehyde (0.5 mmol) at 0 °C. The mixture was allowed to react at 0 °C for 12 h and then was quenched with 1 N HCl (5 mL). The aqueous phase was extracted with ethyl acetate (3 × 5 mL). The combined organic phase was dried over $MgSO_4$, filtered, and concentrated. Chromatography of the residue on silica gel (elution with 5:1 hexane/ethyl acetate) gave the 1-phenylpropanol. The enantiomeric purity of the product was determined by HPLC with a Chiralcel-OD column from Daicel.

General Procedures for the Addition of Et_2Zn to Benzaldehyde Catalyzed by the 4/Ti(O-*i*-Pr)$_4$ System. Under a dry dinitrogen atmosphere, a solution of the complex **4** (0.027 g, 0.025 mmol) and Ti(O-*i*-Pr)$_4$ in 1.5 mL of dry dichloromethane was stirred for 1 h and then 0.75 mL of Et_2Zn (0.75 mmol, 1.0 M solution in hexane) was added at 0 °C. After 30 min, the light yellow solution was treated with benzaldehyde (0.05 mL, 0.50 mmol), stirred at 0 °C for 12 h, and quenched with 1 N HCl (5 mL). The aqueous phase was extracted with ethyl acetate (3 × 5 mL), and the combined organic phase was dried over $MgSO_4$, filtered, and concentrated. Chromatography of the residue on silica gel (elution with 5:1 hexane/ethyl acetate) gave the 1-phenylpropanol as a colorless oil. The enantiomeric purity of the product was determined by HPLC.

Crystal Structure Determinations. An orange crystal of **4** of size 0.4 × 0.6 × 0.6 mm in a sealed capillary under a dinitrogen atmosphere was used for the X-ray diffraction study. Diffraction intensities were collected on a Bruker CCD Smart-1000 diffractometer equipped with graphite-monochromated Mo Kα radiation (λ = 0.71073 Å). All refinements and calculations were carried out with the Bruker AXS SHELXTL software package on a Pentium III-450 computer. Positions of heavy atoms were determined by direct methods, and remaining non-hydrogen atoms were located from successive difference Fourier map calculations. Refinements were carried out using full-matrix least-squares techniques. All non-hydrogen atoms were refined as individual anisotropic atoms. Hydrogen atoms were considered as the riding atom on carbon atoms with a C−H bond length of 0.96 Å, and hydrogen atom temperature factors were fixed at 0.08 Å. Hydrogen atoms were included for refinements in the final cycles.

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Supporting Information Available: X-ray crystallographic data including final coordinates, bond lengths, bond angles, and anisotropic displacement coefficients for complex **4** are available free of charge via the Internet at http://pubs.acs.org.

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