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Achiral Tetrahydrosalen Ligands for the Synthesis of C_2-Symmetric Titanium Complexes: A Structure and Diastereoselectivity Study

Jaume Balsells, Patrick J. Carroll, and Patrick J. Walsh*

Department of Chemistry, University of Pennsylvania, 231 South 34th Street, Philadelphia, Pennsylvania 19104-6323

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Achiral tetrahydrosalen ligands have been employed in the synthesis of chiral C_2-symmetric titanium complexes. When combined with tetrahydrosalen ligands **2a** and **2b**, titanium tetraisopropoxide liberated 2 equiv of isopropyl alcohol and generated the (tetrahydrosalen)Ti(*O*-*i*-Pr)$_2$ complexes **3a** and **3b**. These complexes were shown to be C_2-symmetric by ^{1}H and ^{13}C{^{1}H} NMR spectrometry and X-ray crystallography. X-ray structures of **3a** and **3b** indicate that the bonding of the tetrahydrosalen ligand to titanium is different than the bonding of salen ligands to titanium. Whereas salen ligands usually bind to titanium in a planar arrangement, the tetrahydrosalen is bonded with the phenoxide oxygens mutually *trans*. When bound in this fashion, the nitrogens of the tetrahydrosalen ligand and the titanium become stereogenic centers. The use of titanium complexes of high enantiopurity in the generation of tetrahydrosalen titanium adducts resulted in a maximum diastereoselectivity of 2:1. The diastereoselectivity obtained using chiral titanium alkoxide complexes was greater than the diastereoselectivity observed when a tetrahydrosalen ligand derived from (*S*,*S*)-*trans*-diaminocyclohexane was employed.

Introduction

Several groups have recently begun to explore the potential of achiral ligands that can adopt asymmetric conformations to convey asymmetry in enantioselective catalysts.[1−7] These systems involve the interaction of a chiral ligand (L*) with an achiral ligand (L) in the complex M(L*)L such that the enantiomeric conformations of the unbound achiral ligand become diastereomeric in the coordination sphere of M(L*). In the complex M(L*)L, the achiral ligand can then adopt a chiral conformation and can participate in the transfer of asymmetry from the catalyst to the substrate. Conceptually, catalysts of this type can be divided into two classes on the basis of the magnitude of the barrier to interconversion of the conformations of the achiral ligand. Examples in which the barrier to interconversion of the diastereomeric forms of the achiral ligand in M(L*)L is believed to be low were the first introduced. In ground-breaking work, Katsuki proposed that achiral salen ligands in (salen)Mn-based catalysts existed in enantiomeric forms due to a tilt in the bound salen ligand. The enantiomeric conformations were proposed to interconvert rapidly (Figure 1).[1,2] When resolved *N*-oxide ligands are bonded to the manganese center, the enantiomeric forms of the salen complex become diastereomeric and the equilibrium constant was proposed to favor one of the diastereomers.[3] The resulting complexes have been shown to catalyze the asymmetric epoxidation of certain alkenes with high enantioselectivity. We have used *meso* and achiral bis(sulfonamido) ligands in combination with chiral alkoxide ligands in the asymmetric addition of alkyl groups to aldehydes and demonstrated that modification of the achiral ligand can have a profound effect on the enantioselectivity of the catalyst.[6] A higher barrier to interconversion of the diastereomeric forms of the achiral ligand in M(L*)L was observed with a biphenylphosphine used by Noyori and Mikami[5] in the asymmetric reduction of ketones. Interconversion of the diastereomers through atropisomerism was determined to be slow on the NMR time scale, and an unequal mixture of diastereomeric catalysts was observed. In this system, the difference in the relative rates of these diastereomeric catalysts in the reduction of ketones was large and the faster catalyst was more enantioselective. As a result, a high enantiomeric excess was observed in the asymmetric reduction of ketones. More recent

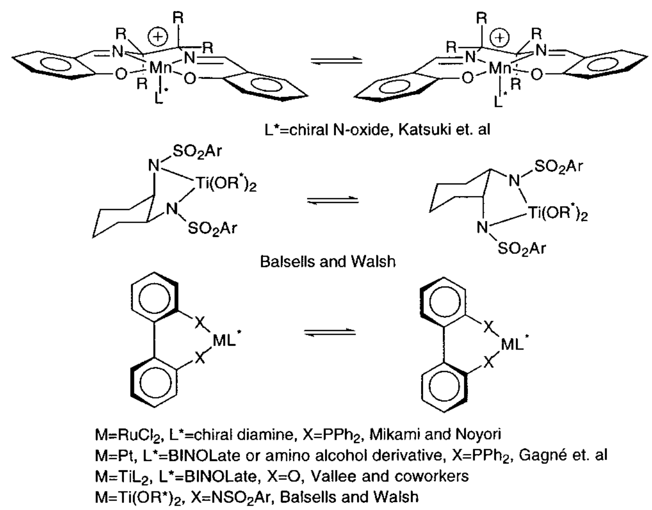

Figure 1. Use of achiral ligands in asymmetric catalysis.

* Corresponding author. E-mail: pwalsh@sas.upenn.edu.

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work has found that the ratio of the diastereomers changes when the sizes of the ligands are modified.[8] Gagné and co-workers have also studied the biphenylphosphine ligand bound to platinum. They provide evidence that the atropisomerization occurs by dissociation of a phosphorus to give a monodentate intermediate that undergoes rotation about the biphenyl C−C bond and demonstrate that this process can be catalyzed by ligands such as pyridine.[9] Vallée[4] and Bolm[10] have employed a titanium system based on resolved BINOL and achiral 2,2′-biphenol derivatives. Although the structure of the active titanium complex is not known, it likely involves both BINOL and the biphenol ligands bound to the metal. This catalyst showed slightly improved enantioselectivity in the carbonyl ene reaction.

If the barrier to interconversion of the diastereomeric conformations of the achiral ligand in M(L*)L is very high, the initial binding of the achiral ligand to the metal center can fix the stereochemistry in the achiral ligand. In this situation, it might be possible to then remove the chiral ligand from M(L*)L to give ML where the achiral ligand L is locked in a chiral conformation when bound to the metal center. The resulting chiral complex ML could then be used in asymmetric catalysis. Examples of enantiopure catalysts composed of ligands that are achiral in the absence of a metal center include planar chiral complexes[11,12] and certain *ansa* metallocene complexes.[13,14]

In this report, we present our preliminary results using tetrahydrosalen ligands bound to titanium(IV). Achiral tetrahydrosalen ligands[15] combine with achiral titanium alkoxides to give C_2-symmetric complexes, the chirality of which is defined by stereogenic nitrogens and the chirality of the titanium. X-ray structures of two such titanium tetrahydrosalen derivatives demonstrate that the compounds are C_2-symmetric in the solid state. A variety of titanium alkoxide and aryloxide derivatives of very high enantiopurity have been combined with achiral tetrahydrosalen ligands. Of those that lead to clean formation of the diastereomeric complexes, the diastereomeric ratio was modest (2:1).

Results and Discussion

We chose to employ the *N,N′*-dimethyltetrahydrosalen ligands **2a** and **2b** for several reasons: they (1) are achiral, (2) are easily prepared, and (3) will bind strongly to titanium, and (4) as binding to titanium occurs, the nitrogens will become stereogenic centers. Several complexes of group VI metals bearing these ligands have been previously synthesized and shown to be C_2-symmetric by NMR and X-ray crystallography.[16−19]

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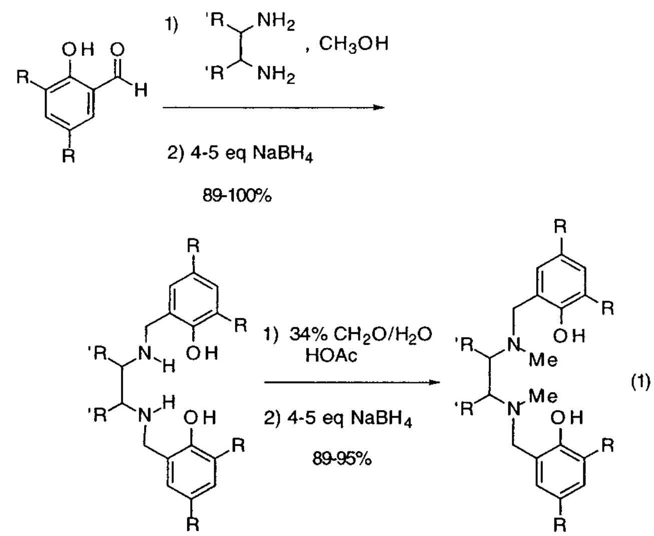
Improved Ligand Synthesis. Previous syntheses of ligands **2a** and **2b** have involved isolation of the salen intermediates and reduction with $NaBH_4$ or $LiAlH_4$, resulting in lower yields.[17,20] Other procedures employ the reductive amination of *N,N′*-dimethylethylenediamine with $NaBH_3(CN)$[16] or a convenient Mannich condensation between formaldehyde, *N,N′*-dimethylethylenediamine, and the phenol (50−70% yield).[21] Synthesis of achiral tetrahydrosalen derivatives **1a** and **1b** and the enantiopure **1c** (derived from (*S,S*)-*trans*-1,2-diaminocyclohexane) was easily accomplished as shown in eq 1. The in situ generation of the Schiff base was followed by reduction with inexpensive and nontoxic $NaBH_4$, giving the product in excellent yield in all cases.



1a, R = H, R′ = H
1b, R = ^{t}Bu, R′ = H
1c, R = ^{t}Bu, R′ = -$(CH_2)_4$-

2a, R = H, R′ = H
2b, R = ^{t}Bu, R′ = H
2c, R = ^{t}Bu, R′ = -$(CH_2)_4$-

Synthesis of Titanium Complexes of Tetrahydrosalen Ligands 2a−c. The synthesis of the titanium complexes proceeded in high yield (eq 2) as is common of simple exchange reactions between titanium alkoxide complexes and alcohols.[22] Addition of titanium tetraisopropoxide to the ligand dissolved in CH_2Cl_2 gave a yellow solution (eq 2). The volatile materials were removed under reduced pressure to give a yellow solid. To ensure complete removal of isopropyl alcohol, the resulting solid was redissolved in CH_2Cl_2 and the volatile materials were again removed. After this procedure was repeated a third time, ^{1}H and ^{13}C{^{1}H} NMR spectra were recorded that showed complete conversion to the titanium complexes **3a** and **3b**. The ligand in these complexes was clearly C_2-symmetric, and no signals that could be attributed to a non-C_2-symmetric isomer were observed. When the ligand **2c** was treated with titanium tetraisopropoxide under identical conditions, the ^{1}H and ^{13}C{^{1}H} NMR spectra indicated that two C_2-symmetric diastereomers had formed in an approximately 1:1 ratio (eq 3). These diastereomers were derived from formation of different

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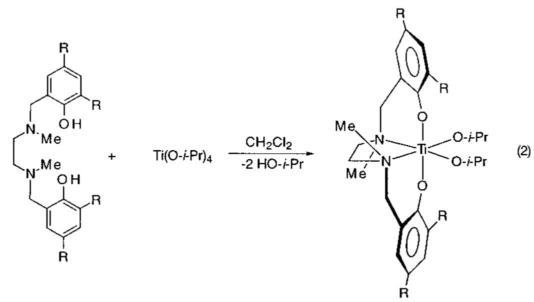
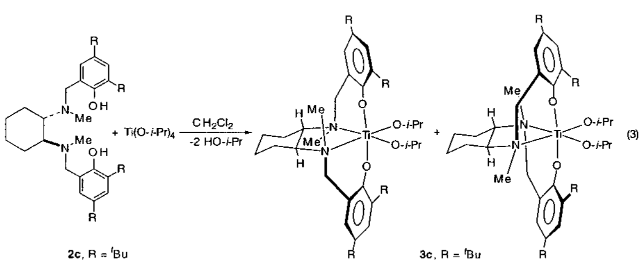
configurations at the nitrogen centers and indicated that the chiral backbone was not effective at dictating the configurations at the nitrogens during the Ti−N bond-forming process.



2a, R = H, R' = H
2b, R = ^{t}Bu, R' = H

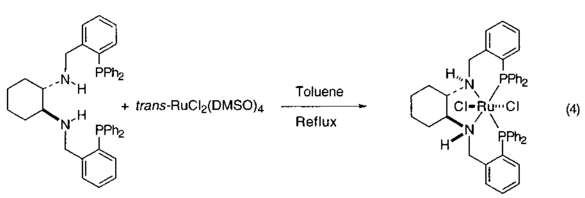
3a, R = H, R' = H
3b, R = ^{t}Bu, R' = H



2c, R = ^{t}Bu

3c, R = ^{t}Bu

The results with the chiral ligand **2c** are in contrast to those reported by Noyori and co-workers involving diamine/diphosphine complexes of ruthenium (eq 4). Reaction of the ligand with $RuCl_2(DMSO)_4$ in refluxing toluene resulted in coordination of the tetradentate ligand to the Ru center. In this reaction, the nitrogens became stereogenic centers upon coordination to ruthenium and only one diastereomer was observed.[23]



X-ray Structure Determinations of 3a and 3b. Salen ligands and related derivatives bound to transition metal complexes have a strong tendency to bind in a planar fashion,[24−31] although exceptions are known.[32−40] To investigate the structure and bonding of the tetrahydrosalen ligand to titanium(IV) and the differences caused by modulating the size of the aryloxy groups, X-ray structural studies of **3a** and **3b** were undertaken. X-ray quality crystals of both **3a** and **3b** were grown by cooling diethyl ether solutions to −20 °C. Data for the structures were collected at low temperature, and the structures of **3a** and **3b** are shown in Figures 2 and 3, respectively.

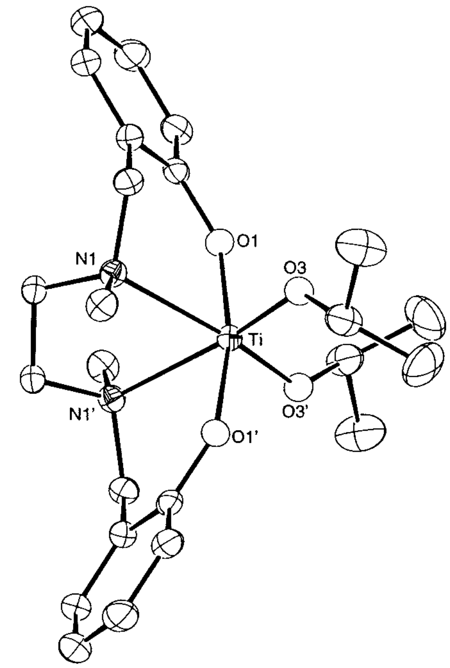


Figure 2. ORTEP drawing of **3a**. Ellipsoids are at the 30% probability level. Selected bond distances and bond angles are listed in Tables 1 and 2, respectively. This molecule has a crystallographically imposed C_2-axis.

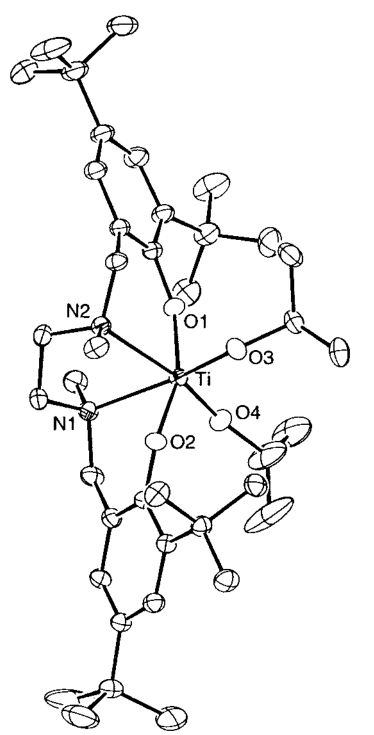


Figure 3. ORTEP drawing of **3b**. Ellipsoids are at the 30% probability level. Selected bond distances and bond angles are listed in Tables 1 and 2, respectively.

The bond distances and bond angles are listed in Tables 1 and 2, respectively, and the data collection parameters are listed in Table 3. Both structures are monomeric with titanium in a distorted octahedral geometry. Unlike salen ligands bound to

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Table 1. Selected Bond Distances (Å) for Compounds **3a** and **3b**

	3a	**3b**
Ti−O(1)	1.9134(15)	1.905(2)
Ti−O(2)		1.914(2)
Ti−O(3)	1.821(2)	1.819(2)
Ti−O(4)		1.780(2)
Ti−N(1)	2.329(2)	2.336(2)
Ti−N(2)		2.353(2)

Table 2. Selected Bond Angles (deg) for **3a**[a] and **3b**

bond angle	**3a**	bond angle	**3b**
O(1)−Ti−O(1′)	168.50(10)	O(1)−Ti−O(2)	161.67(9)
O(1)−Ti−O(3)	97.07(7)	O(1)−Ti−O(3)	95.81(9)
O(1)−Ti−O(3′)	89.88(7)	O(1)−Ti−O(4)	95.14(9)
O(3)−Ti−O(3′)	105.75(11)	O(2)−Ti−O(3)	93.41(9)
O(1)−Ti−N(1)	80.53(6)	O(2)−Ti−O(4)	98.03(10)
O(1)−Ti−N(1′)	90.37(7)	O(3)−Ti−O(4)	103.65(10)
O(3)−Ti−N(1)	89.88(7)	O(1)−Ti−N(1)	88.83(9)
O(3)−Ti−N(1′)	162.63(7)	O(1)−Ti−N(2)	81.35(8)
N(1)−Ti−N(1′)	75.85(9)	O(2)−Ti−N(1)	78.73(8)
		O(2)−Ti−N(2)	82.66(9)
		O(3)−Ti−N(1)	165.94(10)
		O(3)−Ti−N(2)	91.22(9)
		O(4)−Ti−N(1)	89.09(10)
		O(4)−Ti−N(2)	165.02(10)
		N(1)−Ti−N(2)	76.32(9)

[a] Note that **3a** has a crystallographically imposed C_2-symmetry axis.

Table 3. Crystallographic Data and Collection Parameters for **3a** and **3b**

	3a	**3b**
empirical formula	$C_{24}H_{36}N_2O_4T$	$C_{40}H_{68}N_2O_4Ti$
FW	464.45	688.86
space group	*Fdd*2	$P2_1/n$
a, Å	20.7685(3)	14.5777(2)
b, Å	14.2301(3)	10.6529(1)
c, Å	16.9790(4)	26.2556(2)
α, deg	90	90
β, deg	90	93.124(1)
γ, deg	90	90
V, Å^3	5017.9(2)	4071.30(7)
Z	8	4
ρ_{calc}, g/cm	1.230	1.124
T, K	200	210
λ, Å	0.71073	0.71073
μ, mm^{-1}	0.371	0.249
R1[a]	3.15%	7.13%
wR2[b]	7.19%	16.54%

[a] $R1 = \sum||F_o| - |F_c||/\sum|F_o|$. [b] $wR2 = [\sum w(F_o^2 - F_c^2)^2/\sum w(F_o^2)^2]^{1/2}$.

titanium(IV), in which the phenoxy oxygens are *cis*, the phenoxy oxygens in **3a** and **3b** are mutually *trans* with O−Ti−O angles of 168.50(10) and 161.67(9)°, respectively. The difference in bonding between the salen and tetrahydrosalen is a result of the nitrogen geometry. The planar nature of the N═C linkage of the salen causes it to prefer to bind in a square planar fashion, while the saturated backbone of the tetrahydrosalen enforces a nonplanar bonding mode. The isopropoxide groups are *cis*, as are the nitrogens in **3a** and **3b** with O−Ti−O bond angles of 97.07(7) and 93.41(9)°, respectively, and N−Ti−N angles of 75.85(9) and 76.32(9)°, respectively. The structure of **3a** contains a crystallographically imposed C_2-symmetry axis, while **3b** is approximately C_2-symmetric.

The structures are similar to the related zirconium complex, which was published while this work was in progress.[21] Kol and co-workers reported that **1b** reacts with $Zr(CH_2Ph)_4$ to give the expected (tetrahydrosalen)$Zr(CH_2Ph)_2$. This compound is also C_2-symmetric with *trans* phenoxide oxygens. In the presence of $B(C_6F_5)_3$, (tetrahydrosalen)$Zr(CH_2Ph)_2$ will promote the efficient, isospecific living polymerization of 1-hexene.[21] The gross structural features of **3a** and **3b** are also reminiscent of the molybdenum complexes of tetrahydrosalen (tetrahydrosalen)Mo(O)$_2$.[16−19] The (tetrahydrosalen)MoO_2 complexes are C_2-symmetric with *trans* phenoxide oxygens. The titanium phenoxide Ti−O distances in **3a** and **3b** range from 1.905 to 1.914 Å, longer than titanium phenoxide distances in four-coordinate complexes of the type $(ArO)_2TiX_2$ (1.7−1.8 Å).[41−43] The titanium phenoxide Ti−O distances in **3a** and **3b** are longer than the terminal Ti−O distances in the octahedral dimeric $[Ti(OPh)_4(HOPh)]_2$ (1.789−1.884 Å)[44] but similar to those in octahedral titanium salen complexes (salen)TiX_2 (X = Me, Cl, OAr), which range from 1.829 to 1.899 Å.[29−31] The titanium-isopropoxy Ti−O distances are within the expected range.[22] The Ti−N distances for **3a** and **3b** range from 2.329 to 2.353 Å. These distances are longer than those found in the salen complex (salen)Ti(OAr)$_2$ of 2.147−2.168 Å[29] and longer than those found in the diamine adduct $(ArO)_2$Ti(diamine)Cl_2 of 2.273 Å.[45]

Reactions of Tetrahydrosalen Ligands with Enantiopure Ti(OR*)$_4$. In analogy with the synthesis of the (tetrahydrosalen)-Ti(*O*-*i*-Pr)$_2$ complexes, tetrahydrosalen ligands **2a** and **2b** were combined with Ti(OR*)$_4$ containing alkoxide ligands of >99% enantiomeric excess (ee) to determine the extent to which the alkoxide ligands control the stereochemistry of the binding of the tetrahydrosalen ligands. Titanium alkoxide complexes of two types were used. Those containing mixed alkoxide or diolate ligands, Ti(OR*)$_2$(*O*-*i*-Pr)$_2$ or Ti(diolate*)(*O*-*i*-Pr)$_2$, allow the equilibrium to be driven toward the tetrahydrosalen titanium complexes with chiral alkoxide ligands by removal of the isopropyl alcohol under reduced pressure. The second type of enantiopure titanium complexes was the homoleptic alkoxide complexes Ti(OR*)$_4$. The results obtained with the mixed alkoxide complexes Ti(OR*)$_2$(*O*-*i*-Pr)$_2$ are shown in Table 4. In these reactions, the isopropyl alcohol was removed as described earlier. Under the reaction conditions employed, several of the mixed alkoxide complexes resulted in the formation of complex mixtures of products, presumably due to the multidentate ligands bonding to more than one titanium center.

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Table 4. Ratio of Diastereomers Formed upon Reactions of **2a** and **2b** with Mixed Alkoxide Complexes

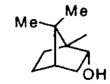
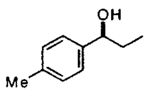
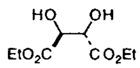
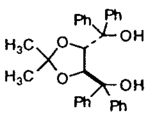
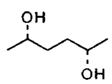
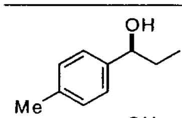
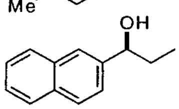
$Ti(OR^*)_2(O\text{-}i\text{-}Pr)_2$ R*OH =		Diastereomeric Ratio T=1h	Diastereomeric Ratio T=24h
	2a[a]	1 : 1	1 : 1
	2b	1 : 1	
	2a	complex mixture	
	2b	complex mixture	
(*S*)-BINOL	2a	complex mixture	
	2b	complex mixture	
	2a	complex mixture	
	2a	1 : 1	
	2b	complex mixture	
	2a[b]	1 : 1	1.8 : 1
	2b	complex mixture	

Table 5. Ratio of Diastereomers Formed upon Reaction of **2a** with Homoleptic Alkoxide Complexes

$Ti(OR^*)_4$ R*OH =		Diastereomeric Ratio T = 0	Diastereomeric Ratio T = 24h
	2a	1 : 1	2 : 1
	2a	1 : 1	1.7 : 1

Alkoxide complexes of the type $Ti(OR^*)_2(O\text{-}i\text{-}Pr)_2$, derived from (*S*)-1-(4-tolyl)-1-propanol, (*S*)-BINOL, and (*R*,*R*)-diethyl tartrate, gave mixtures with both ligands **2a** and **2b**. Titanium alkoxide complexes derived from (*S*,*S*)-TADDOL and (*S*,*S*)-2,4-hexadiol both gave 1:1 mixtures of the diastereomers when combined with **2a** as determined by integration of ^{1}H NMR spectra after 1 h of reaction at room temperature. As shown in Table 4, the reaction employing (TADDOLate)$Ti(O\text{-}i\text{-}Pr)_2$ was very clean and both diastereomers were observed in a 1:1 ratio. However, under identical conditions, reaction of the diolate complex derived from (*S*,*S*)-2,4-hexandiol resulted in the formation of multiple products.

The titanium tetraalkoxide complexes $Ti(OR^*)_4$ proved to be more amenable for the synthesis of the (tetrahydrosalen)Ti-$(OR^*)_2$ complexes. As shown in Table 5, the use of the alkoxide complexes derived from (*S*)-1-(4-tolyl)-1-propanol and (*S*)-1-(2-naphthyl)-1-propanol with **2a** resulted in the initial formation of a 1:1 mixture of diastereomers. However, these mixtures equilibrated over 24 h to give 2:1 and 1.7:1 ratios of the diastereomers (Table 5). No further change was observed after 48 h, indicating that equilibrium had been achieved. It is likely that the equilibration of the diastereomers was promoted by the liberated alcohol. One possible mechanism begins with the protonation of the (tetrahydrosalen)$Ti(OR^*)_2$ at the phenoxide oxygen by alcohol to give a titanium alkoxide. This could allow reversible dissociation of the phenol and nitrogens. The rebonding of the nitrogens and phenol, followed by proton transfer to the alkoxide and liberation of the alcohol, would scramble the configurations at the nitrogens and eventually lead to formation of the thermodynamic mixture of diastereomers. In an attempt to increase the diastereomeric excess of the (tetrahydrosalen)titanium bis(borneolate) complex, we added 2 equiv of borneol. However, no change in the equilibrium was observed over 48 h (^{1}H NMR).

It is interesting to compare the results in Table 5 to those obtained with the chiral tetrahydrosalen ligand **2c**. The effect of the chiral *trans*-1,2-diaminocyclohexane backbone in ligand **2c** on the diastereoselectivity of the bonding to titanium in **3c** was less than that observed in the binding of **2a** to $Ti(OR^*)_4$. Addition of 2 equiv of isopropyl alcohol to **3c** did not result in a change in the diastereomeric ratio. It is possible that the origin of the low diastereoselectivity in the binding of ligands **2a**−**c** to $Ti(OR^*)_4$ complexes is that the methyl and methylene groups of the ligand have similar sizes.

In conclusion, coordination of an achiral ligand to an achiral metal can result in formation of a chiral complex if a ligating center becomes stereogenic upon coordination or if the metal becomes a stereogenic center upon the coordination of the achiral ligand.[46] Examples are known where the chirality of the ligands can be used to control the stereochemistry at a metal center.[46−51] Recently, sulfoxides of high enantiopurities have been added to racemic $(bipy)_2RuCl_2$ complexes to generate sulfoxide adducts with good diastereoselectivity.[52,53] In the system presented here, we have attempted to establish the stereochemisty at two nitrogens in the ligand and at the titanium center.

In this work achiral tetrahydrosalen ligands have been applied to the diastereoselective synthesis of a series of titanium complexes. The synthesis of the ligands has been optimized, and the ligands are now prepared in a two-step reaction sequence in excellent yield. We have shown that these ligands react with titanium tetraisopropoxide to generate (tetrahydrosalen)$Ti(O\text{-}i\text{-}Pr)_2$ complexes **3a** and **3b**, which are chiral at the nitrogens and at the titanium. Both complexes are C_2-symmetric as demonstrated by NMR spectrometry and X-ray crystallography. Diastereoselective syntheses were performed with chiral titanium alkoxide complexes that gave diastereomeric ratios of up to 2:1. In this diastereoselective reaction, three new stereogenic centers are created. Although the diastereomeric ratios were not high, they were higher than those observed when ligand **2c**, which has a chiral *trans*-1,2-diaminocyclohexane backbone, was employed. We are currently optimizing related achiral ligands that have the potential to give higher diastereoselectivity and may prove useful in asymmetric catalysis.

Experimental Section

General Considerations. All manipulations involving titanium alkoxides were carried out under an inert atmosphere in a Vacuum Atmospheres drybox with an attached MO-40 Dritrain or by using

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standard Schlenk or vacuum line techniques. Solutions were degassed as follows: they were cooled to −196 °C, evacuated under high vacuum, and thawed. This sequence was repeated three times in each case. ^{1}H NMR spectra were obtained on either the Bruker 200 or 500 MHz Fourier transform NMR spectrometer at the University of Pennsylvania NMR facility. ^{1}H NMR spectra were recorded relative to residual protiated solvent. ^{13}C{^{1}H} NMR spectra were obtained at either 50 or 125 MHz on the 200 or 500 MHz instrument, respectively, and chemical shifts were recorded relative to the solvent resonance. Chemical shifts are reported in units of parts per million downfield from tetramethylsilane, and all coupling constants are reported in Hertz. IR spectra were obtained on a Perkin-Elmer 1600 series spectrometer. Unless otherwise specified, all reagents were purchased from Aldrich Chemical Co. and used without further purification. Titanium tetraisopropoxide and (*S*)-2-tolyl-1-propanol (99% ee) were distilled under vacuum and stored in glass vessels sealed with Teflon stoppers.

Hexanes (UV grade, alkene free) were distilled from sodium benzophenone ketyl/tetraglyme under nitrogen. Benzene, toluene, diethyl ether, and THF were distilled from sodium benzophenone ketyl under nitrogen. Dichloromethane was distilled from calcium hydride under nitrogen. Deuterated solvents (purchased from Cambridge Isotopes) for use in NMR experiments were dried in the same manner as their protiated analogues but were vacuum transferred from the drying agent. $CDCl_3$ was dried over calcium hydride and vacuum transferred.

Synthesis and Characterization of Ligands 1a−2c. Preparation of 1a. To a stirred solution of salicylaldehyde (2.24 g, 20 mmol) in 10 mL of methanol was slowly added a solution of ethylenediamine (601 mg, 10 mmol) in 30 mL of methanol, and the mixture was stirred for 5 min. Sodium borohydride (1.51 g, 40 mmol) was then added in small portions. When the mixture was colorless, it was poured over 100 mL of water and extracted with dichloromethane. The combined organic phases were dried, and the solvents were removed in vacuo to obtain **1a** as a white solid. The yield was 98% (2.68 g, 9.84 mmol): mp 117 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.82 (s, 4H), 3.97 (s, 4H), 6.77 (td, J_1 = 7.4 Hz, J_2 = 1.0 Hz, 2H), 6.82 (d, J = 8.0 Hz, 2H), 6.96 (d, J = 7.4 Hz, 2H), 7.16 (td, J_1 = 8.0 Hz, J_2 = 1.6 Hz, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz) δ 47.8 (2CH_2), 52.6 (2CH_2), 116.4 (2CH), 119.2 (2CH), 122.1 (2C), 128.4 (2CH), 128.9 (2CH), 157.9 (2C); IR (KBr) 3275, 2860, 1617, 1590, 1496, 1466, 1413, 1256, 1100, 964, 746 cm^{-1}; MS (ES(+), 30 eV) *m/z* 273 (M + H, 65%), 295 (M + Na, 100%), 567 (2M + Na, 90%).

Preparation of 1b. Ligand **1b** was prepared by the same procedure as **1a**. Reduction of the imine required 5 equiv of sodium borohydride and overnight stirring. The yield was 91% (4.51 g, 9.1 mmol): mp 174 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.28 (s, 18H), 1.41 (s, 18H), 2.86 (s, 4H), 3.96 (s, 4H), 6.84 (d, J = 2.4 Hz, 2H), 7.22 (d, J = 2.4 Hz, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz) δ 29.6 (6CH_3), 31.7 (6CH_3), 34.1 (2C), 34.9 (2C), 48.0 (2CH_2), 53.5 (2CH_2), 121.7 (2C), 123.1 (2CH), 123.2 (2CH), 136.0 (2C), 140.6 (2C), 154.4 (2C); IR (KBr) 3312, 2959, 2868, 1605, 1480, 1359, 1236, 1105, 966, 880 cm^{-1}; MS (ES(+), 30 eV) *m/z* 497.7 (M + H, 100%), 519.8 (M + Na, 55%).

Preparation of 1c. Ligand **1c** was prepared by the same procedure as **1a**. Reduction of the imine required 5 equiv of sodium borohydride and overnight stirring. The yield was 100% (1.56 g, 2.83 mmol): mp 140 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.2−1.3 (m, 4H), 1.27 (s, 18H), 1.37 (s, 18H), 1.70−1.75 (m, 2H), 2.1−2.2 (m, 2H), 2.4−2.5 (m, 2H), 3.90, 4.03 (AB, J = 13.3 Hz, 4H), 6.86 (d, J = 2.3 Hz, 2H), 7.21 (d, J = 2.3 Hz, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz) δ 24.1 (2CH_2), 29.6 (6CH_3), 30.7 (2CH_2), 31.7 (6CH_3), 34.1 (2C), 34.9 (2C), 50.9 (2CH_2), 59.9 (2CH_2), 122.4 (2C), 123.0 (2CH), 123.1 (2CH), 136.0 (2C), 140.6 (2CH), 154.4 (2C); IR (KBr) 3294, 2958, 2862, 1605, 1481, 1361, 1236, 875 cm^{-1}; MS (ES(−), 30 eV) *m/z* 549.5 (M − H, 100%), 585.5 (M + Cl, 30%).

Preparation of 2a. This ligand has been previously prepared.[16] To a solution of **1a** (1.8 g, 6.61 mmol) in acetonitrile (110 mL) and acetic acid (15 mL) was added formaldehyde (5.45 mL, 68.8 mmol, 37% in water), and the mixture was stirred for 20 min. Sodium borohydride (1.1 g, 29.36 mmol) was added, and the reaction mixture was stirred at room temperature for 12 h. Acetonitrile was removed in vacuo, and the residue was hydrolyzed with 2 N NaOH. The aqueous phase was extracted with dichloromethane; the organic phase was dried, and the solvents were removed under reduced pressure. The resulting residue was purified by chromatography (silica gel, hexanes/ethyl acetate) to obtain **2a** as a white solid. The yield was 89% (1.79 g, 5.9 mmol): mp 84 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.28 (s, 6H), 2.66 (s, 4H), 3.69 (s, 4H), 6.77 (td, J_1 = 7.0 Hz, J_2 = 1.0 Hz, 2H), 6.82 (dd, J_1 = 8.1 Hz, J_2 = 1.0 Hz, 2H), 6.95 (dd, J_1 = 7.0 Hz, J_2 = 1.6 Hz, 2H), 7.16 (td, J_1 = 8.0 Hz, J_2 = 1.6 Hz, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz) δ 41.7 (2CH_3), 54.1 (2CH_2), 61.8 (2CH_2), 116.2 (2CH), 119.1 (2CH), 121.6 (2C), 128.5 (2CH), 128.9 (2CH), 157.8 (2C); IR (KBr) 2963, 2841, 1610, 1586, 1474, 1407, 1256, 1192, 1099, 1015, 754 cm^{-1}; MS (ES(+), 30 eV) *m/z* 323 (M + Na, 55%), 623 (2M + Na, 100%).

Preparation of 2b. This ligand has been previously prepared.[21] Ligand **2b** was prepared by the same procedure as **2a**. The yield was 95% (3.5 g, 6.67 mmol): mp 142 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.27 (s, 18H), 1.39 (s, 18H), 2.26 (s, 6H), 2.63 (s, 4H), 3.66 (s, 4H), 6.79 (d, J = 2.3 Hz, 2H), 7.20 (d, J = 2.3 Hz, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz) δ 29.6 (6CH_3), 31.7 (6CH_3), 34.1 (2C), 34.8 (2C), 41.6 (2CH_3), 53.8 (2CH_2), 62.7 (2CH_2), 121.0 (2C), 123.0 (2CH), 123.3 (2CH), 135.6 (2C), 140.5 (2C), 154.2 (2C); IR (KBr) 2951, 2905, 1604, 1480, 1423, 1233, 1202, 876 cm^{-1}; MS (ES(+), 30 eV) *m/z* 525.9 (M + H, 40%), 609.7 (100%).

Preparation of 2c. Ligand **2c** was prepared by the same procedure as **2a**. The yield was 93% (1.27 g, 2.20 mmol): mp 100 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.0−1.2 (m, 4H), 1.34 (s, 18H), 1.43 (s, 18H), 1.75−1.85 (m, 2H), 2.0−2.1 (m, 2H), 2.75 (s, 6H), 2.7−2.8 (m, 2H), 3.80−4.0 (m, 4H), 6.86 (s, 2H), 7.21 (s, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz) δ 22.6 (2CH_2), 25.3 (2CH_3), 29.6 (6CH_3), 31.7 (6CH_3), 34.1 (2CH_2), 34.9 (2C), 58.7 (2CH_2), 61.4 (2CH_2), 121.3 (2C), 122.7 (2CH), 123.5 (2CH), 135.5 (2C), 140.2 (2CH), 154.4 (2C); one quaternary carbon was not observed; IR (KBr) 2953, 2864, 1605, 1481, 1360, 1234, 877 cm^{-1}; MS (ES(−), 30 eV) *m/z* 577.6 (M − H, 60%), 675 (100%).

Preparation of Titanium Complexes. Preparation of 3a. To a solution of ligand **2a** (150 mg, 0.5 mmol) in 5 mL of dichloromethane was added titanium isopropoxide (142 mg, 0.5 mmol). The solution became yellow. The solvent was removed in vacuo, and the resulting solid was redissolved in dichloromethane. This process was repeated a total of three times to ensure complete removal of isopropyl alcohol. **3a** was obtained as a yellow solid in 99% yield (230 mg, 0.49 mmol). Crystals of **3a** suitable for X-ray analysis were obtained by cooling an ethereal solution of **3a** to −20 °C: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.30 (d, J = 6.2 Hz, 6H), 1.31 (d, J = 6.2 Hz, 6H), 1.82 (d, J = 9.4 Hz, 4H), 2.50 (s, 6H), 3.02 (d, J = 9.4 Hz, 4H), 3.17 (d, J = 13.4 Hz, 4H), 4.69 (d, J = 13.4 Hz, 4H), 5.08 (qui, J = 6.2 Hz, 2H), 6.71 (d, J = 7.5 Hz, 2H), 6.72 (t, J = 7.5 Hz, 2H), 6.99 (d, J = 7.5 Hz, 2H), 7.20 (td, J_1 = 7.5 Hz, J_2 = 1.5 Hz, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz) δ 25.6 (2CH_3), 25.9 (2CH_3), 47.1 (2CH_3), 51.7 (2CH_2), 64.5 (2CH_2), 77.8 (2CH), 117.4 (2CH), 117.5 (2CH), 124.5 (2C), 129.0 (2CH), 129.3 (2CH), 162.0 (2C). Anal. Calcd for $C_{24}H_{36}N_2O_4Ti$: C, 62.07; H, 7.81; N, 6.03. Found: C, 61.97; H, 7.84; N, 5.80.

Preparation of 3b. Complex **3b** was prepared by the same procedure as **3a**. The yield was 95% (124 mg, 0.18 mmol): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.10 (d, J = 6.0 Hz, 6H), 1.25 (d, J = 6.0 Hz, 6H), 1.33 (s, 18H), 1.57 (s, 18H), 1.88 (d, J = 9.1 Hz, 4H), 2.52 (s, 6H), 3.17 (d, J = 13.4 Hz, 4H), 3.24 (d, J = 9.1 Hz, 4H), 4.48 (d, J = 13.4 Hz, 4H), 4.86 (qui, J = 6.0 Hz, 2H), 6.82 (d, J = 2.5 Hz, 2H), 7.26 (d, J = 2.5 Hz, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz) δ 26.3 (2CH_3), 26.7 (2CH_3), 30.4 (6CH_3), 31.8 (6CH_3), 34.1 (2C), 35.2 (2C), 48.7 (2CH_3), 52.5 (2CH_2), 65.5 (2CH_2), 77.1 (2CH), 122.9 (2C), 123.1 (2CH), 123.9 (2CH), 135.7 (2C), 138.3 (2C), 159.3 (2C). Anal. Calcd for $C_{40}H_{68}N_2O_4Ti$: C, 69.74; H, 9.95; N, 4.07. Found: C, 69.84; H, 10.41; N, 4.02.

Preparation of 3c. Complex **3c** was prepared by the same procedure as **3a**. It was obtained as a 1:1 mixture of diastereoisomers. The yield was 99% (128 mg, 0.173 mmol): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.01 (d, J = 6.0 Hz, 6H), 1.09 (s, 18H), 1.22 (d, J = 6.0 Hz, 6H), 1.25 (d, J = 6.0 Hz, 6H), 1.28 (d, J = 6.0 Hz, 6H), 1.1−1.5 (m, 4H + 4H), 1.34 (s, 18H), 1.35 (s, 18H), 1.56 (s, 18H), 1.80−2.4 (m, 6H + 6H), 2.66 (s, 6H), 2.84 (s, 6H), 3.07 (td, J_1 = 11.7 Hz, J_2 = 3.7 Hz, 2H), 3.19 (td, J_1 = 11.5 Hz, J_2 = 4.2 Hz, 2H), 3.34 (d, J = 13.1 Hz, 4H), 3.60 (d, $J = 14.1$ Hz, 4H), 4.43 (d, $J = 13.1$ Hz, 4H), 4.57 (d, $J = 14.1$ Hz, 4H), 4.88 (qui, $J = 6.0$ Hz, 2H), 5.11 (qui, $J = 6.0$ Hz, 2H), 6.76 (d, $J = 2.2$ Hz, 2H), 6.81 (d, $J = 2.2$ Hz, 2H), 7.21 (d, $J = 2.2$ Hz, 2H), 7.25 (d, $J = 2.2$ Hz, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 22.3, 23.8, 24.3, 25.3, 26.0, 26.4, 27.0, 27.1, 30.2, 30.3, 31.7, 31.8, 34.0, 34.1, 34.5, 35.1, 44.2, 47.0, 56.6, 58.5, 62.8, 66.4, 75.4, 76.2, 121.6, 122.0, 123.2, 123.3, 124.3, 124.7, 135.2, 135.9, 137.4, 138.9, 158.5, 159.2.

General Procedure for the Preparation of Titanium Complexes of Tetrahydrosalen Ligands and Chiral Alcohols. To a solution of TADDOL (50 mg, 0.107 mmol) in 2 mL of dichloromethane was added titanium isopropoxide (30.5 mg, 0.107 mmol). The colorless solution was stirred for 5 min, and vacuum was applied to the system to remove volatile components. The residue was dissolved in 2 mL of dichloromethane. This procedure was repeated three times to ensure removal of isopropyl alcohol. The final residue was dissolved in 2 mL of dichloromethane, and a solution of ligand **2a** (50 mg, 0.107 mmol) in 2 mL of dichloromethane was added via cannula. Vacuum was applied to the yellow solution to remove volatile materials, and the residue was redissolved in 2 mL of dichloromethane. This procedure was repeated three times to ensure removal of isopropyl alcohol. The diastereomeric ratio of the resulting complex was evaluated by ^1H NMR spectrometry.

Preparation of Titanium Complexes of Tetrahydrosalen Ligands Using Ti(OR*)$_4$.[6] To a solution of ligand **2a** (30 mg, 0.1 mmol) in 2 mL of dichloromethane was added a solution of titanium tetra-(*S*)-1-tolylpropoxide (0.66 mL, 0.15 M) in dichloromethane. The resulting yellow solution was stirred for 5 min, and the solvent was removed in vacuo. The diastereomeric ratio of the resulting complex was evaluated by ^1H NMR. The freshly prepared complex consisted of a 1:1 mixture of diastereomers as determined by integration of the ^1H NMR spectrum. When the equilibrium was reached (24 h), ^1H NMR was consistent with a 2:1 mixture of the diastereomers.

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Supporting Information Available: Experimental details, tables, and structure representations, and X-ray crystallographic files in CIF format for complexes **3a** and **3b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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