

Atropisomeric Amides: Achiral Ligands With Chiral Conformations

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Dedicated to Professor K. Barry Sharpless, recipient of the 2000 Chirality Medal

ABSTRACT A new class of achiral ligands with atropisomeric conformations has been coordinated to titanium(IV). The ligands are *ortho*-hydroxy benzamide derivatives which are deprotonated on reaction with titanium tetraisopropoxide to furnish $\text{Ti}(\text{L})_2(\text{O-}i\text{Pr})_2$ complexes ($\text{L}=\textit{ortho}$ -phenoxy benzamide). In these octahedral titanium compounds, the *ortho*-phenoxy benzamide ligands chelate to titanium, bonding through the phenoxide oxygen and the amide carbonyl oxygen. The benzamide ligands adopt atropisomeric conformations with an angle between the aryl and amide groups of approximately 35° . The ligand precursor, ligand, and titanium complexes have been characterized by X-ray crystallography. Only one diastereomer of each titanium complex was observed in the solid state structures. *Chirality* 15:615–621, 2003. © 2003 Wiley-Liss, Inc.

KEY WORDS: atropisomeric amides; titanium; stereochemistry; alkoxide; X-ray structure

The traditional approach to asymmetric catalysis with metal-based catalysts is an iterative operation that revolves around the synthesis of chiral ligands of high enantiopurity.^{1–3} Once the chiral ligands have been bound to the metal center, the new catalysts are examined to determine their enantioselectivities and activities. Results of these studies are evaluated and the next generation of ligands is designed. In this process, the key to efficient reaction optimization is often rapid access to numerous catalysts with diverse chiral environments. Unfortunately, the synthesis of enantiopure ligands can be an arduous task, severely hampering the optimization of the asymmetric process.⁴

A different approach to asymmetric catalysis is the use of an enantiopure ligand (L^*) in combination with achiral or *meso*-ligands (L) in a catalyst $\text{M}(\text{L})\text{L}^*$. The degree of interaction between the chiral ligand and the achiral or *meso*-ligand in the complex $\text{M}(\text{L})\text{L}^*$ depends on the nature and the proximity of the ligands. The enantiomeric conformations of the achiral or *meso*-ligand in ML become diastereomeric in $\text{M}(\text{L})\text{L}^*$ and differ in energy. If the interactions between L and L^* are strong, the chiral ligand L^* can bias the conformation of the achiral or *meso*-ligand L such that it preferentially adopts one of the two enantiomeric conformations. The chiral conformation of L can play an integral part, or a dominant role, in the transmission of asymmetry from the catalyst to the substrate.^{5–11} The advantage of this approach to asymmetric catalysis over the traditional approach is that catalysts can be optimized by the synthesis of achiral and *meso*-ligands instead of homochiral ligands.^{5,9–11} In general, achiral ligands are more easily prepared than enantiopure ligands and are significantly less costly.

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To facilitate optimization of asymmetric catalysts with normally unresolvable ligands with chiral conformations, additional ligands of this class must be prepared and their behavior studied. In this report, we introduce stereochemically dynamic ligands that possess atropisomeric conformations when bound to a transition metal. The ligands of interest are *ortho*-hydroxy benzamides. We have investigated the atropisomeric conformations in the solid state structure of the ligand precursor, the unbound ligand, and the ligand chelated to a Lewis acidic titanium center.

EXPERIMENTAL

General Methods

All reactions were carried out under a nitrogen atmosphere with oven-dried glassware and their progress was monitored by thin-layer chromatography (TLC) to ensure the reactions had reached completion. All manipulations involving titanium alkoxides were carried out using an inert atmosphere in a Vacuum Atmosphere drybox with an attached MO-40 DriTrain or by using standard Schlenk or vacuum line techniques. Dichloromethane, toluene, and hexanes were dried through alumina columns. Tetrahydrofuran was dried and distilled from sodium benzophenone ketyl and stored under N_2 in a glass vessel sealed with a Teflon stopper. Titanium tetraisopropoxide was distilled

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under vacuum and stored under N_2 in a glass vessel sealed with a Teflon stopper. Unless otherwise specified, all chemicals were obtained from Acros or Aldrich (Milwaukee, WI) and all solvents were purchased from Fischer Scientific (Pittsburgh, PA). Deuterated chloroform for NMR spectrometry was dried over calcium hydride, degassed, and vacuum transferred before use. The 1H NMR and $^{13}C\{^1H\}$ NMR spectra were run on a Bruker AC-360 Fourier transform NMR spectrometer at 360 MHz and 90 MHz, respectively. Chemical shifts are reported in units of parts per million downfield from tetramethylsilane and all coupling constants are reported in Hertz. The infrared spectra were obtained using KBr pellets on a Perkin-Elmer (Norwalk, CT) 1600 series spectrometer. TLC was performed on Whatman (Clifton, NJ) Aluminum Silica Gel/UV 250 μm plates and visualized by ultraviolet light or by staining with anisaldehyde stain or phosphomolybdic acid stain. Silica gel (230–400 mesh, Silicycle) was used for air-flashed chromatography.

General procedure for preparation of *N,N*-dialkylmethoxybenzamides. All the *N,N*-dialkylmethoxybenzamides were prepared following the procedure of Yus and co-workers.⁶² To a round bottom flask containing *ortho*-anisic acid (3.00 g, 19.7 mmol) was added excess $SOCl_2$ (7.19 mL, 98.6 mmol, 5 equiv.) under nitrogen. A catalytic quantity of dry DMF (two to three drops) was added and the reaction mixture was heated at 50°C for 4 h under nitrogen. The excess $SOCl_2$ was removed under reduced pressure. The resulting clear to slightly brown oil was dissolved in dry dichloromethane (20 mL) and was cooled to 0°C. A solution of the corresponding amine (23.7 mmol, 1.2 equiv.) and Et_3N (4.12 mL, 29.6 mmol, 1.5 equiv.) in dry dichloromethane was added dropwise to the acid chloride solution, generally resulting in a cream to white precipitate. The reaction mixture was allowed to warm to room temperature and was stirred overnight. The resulting mixture was quenched with water (6 mL), extracted with ethyl acetate (2 \times 40 mL), and successively washed with 2N HCl (2 \times 40 mL) and saturated $NaHCO_3$ (2 \times 40 mL). The organic layer was dried over anhydrous Na_2SO_4 . The volatiles were removed under reduced pressure and the resulting residue was purified by either column chromatography or recrystallization to yield the desired amide.

***N,N*-Di-*iso*-propyl-2-methoxybenzamide (4a).** Compound **4a** has been previously synthesized.⁶² The compound was prepared following the general procedure. Di-*iso*-propylamine (3.31 mL, 23.7 mmol, 1.2 equiv.) was used and the crude amide was recrystallized by layering a dichloromethane solution of the compound with hexanes to give pale yellow crystals of **4a** in 92% yield (4.26 g, 18.1 mmol). The 1H NMR and $^{13}C\{^1H\}$ NMR spectra of the product are in agreement with those in the literature.

***N,N*-Diphenyl-2-methoxybenzamide (4b).** Compound **4b** has been previously synthesized⁶³; however, no 1H NMR and $^{13}C\{^1H\}$ NMR data were published. The compound was prepared following the general procedure. Diphenylamine (3.34 g, 19.8 mmol, 1.2 equiv.) was used and the crude purple-black solid was purified by flash column chromatography followed by recrystallization from dichloro-

methane to afford pale yellow crystals in 83% yield (4.16 g, 13.7 mmol). 1H NMR (360 MHz, $CDCl_3$) δ 7.70–7.00 (br m, 12H), 6.85 (t, $J = 7.4$ Hz, 1H), 6.61 (d, $J = 8.3$ Hz, 1H), 3.60 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (90 MHz, $CDCl_3$) δ 169.3, 155.4, 143.2, 130.9, 129.4, 128.7 (br), 127.6 (br), 126.9, 126.5, 120.5, 110.8, 55.3 ppm.

General procedure for demethylation of the *N,N*-dialkylmethoxybenzamides. All the *N,N*-dialkylmethoxybenzamides were demethylated following the procedure of Katzenellenbogen and co-workers.⁶⁴ To a solution of the *N,N*-dialkylmethoxybenzamide in dry dichloromethane under nitrogen at $-78^\circ C$ was added BBr_3 (3 equiv.) dropwise. The reaction was allowed to reach room temperature and stirred overnight. The complete disappearance of the starting material was monitored by TLC. The reaction mixture was cooled to 0°C in an ice bath and quenched with ice-cold water (5 mL). The reaction mixture was extracted with diethyl ether, washed with brine, and dried over Na_2SO_4 . The volatiles were removed under reduced pressure and the resulting residue was purified by recrystallization from appropriate solvents to afford the desired phenolic compounds.

***N,N*-Di-*iso*-propyl-2-hydroxybenzamide (5a).** Compound **5a** has been previously synthesized using the anionic Fries rearrangement.³⁷ The compound was prepared following the general procedure. The crude product was recrystallized from dichloromethane and hexanes to afford the desired phenol **5a** as an off-white powder in 86% yield (1.70 g, 7.22 mmol). The 1H NMR and $^{13}C\{^1H\}$ NMR spectra are in agreement with those in the literature.³⁷

***N,N*-Diphenyl-2-hydroxybenzamide (5b).** Compound **5b** has been synthesized previously using phenyl salicylate and diphenylamine.⁶⁵ The compound was prepared following the general procedure. Demethylation of **4b** (1.00 g, 3.31 mmol) required 6 equiv. of BBr_3 (1.9 mL, 20.1 mmol) and the reaction was refluxed for 3 days. The reaction was quenched with ice-cold water and the aqueous layer was basified with 2M NaOH solution. The basic aqueous layer was washed once with diethyl ether (10 mL), then acidified by adding concentrated HCl dropwise until a white precipitate appeared and the aqueous solution was acidic by pH paper. The resulting precipitate was washed with cold distilled water and hexanes and was recrystallized from dichloromethane to give the desired phenol **5b** as pale yellow crystals in 71% yield (0.68 g, 2.35 mmol). The 1H NMR and $^{13}C\{^1H\}$ NMR spectra of the product are in agreement with those in the literature.⁶⁵

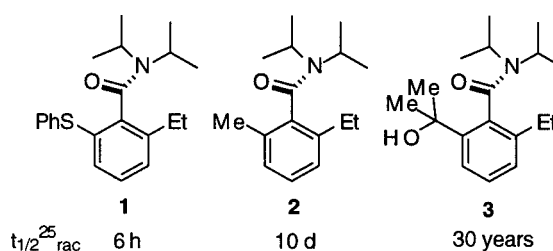
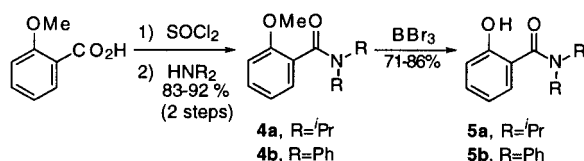


Fig. 1. Half-lives for racemization of atropisomeric amides at room temperature.



Scheme 1. Synthesis of amides 4 and 5.

General procedure for the preparation of titanium complexes. Titanium isopropoxide (1 equiv.) was added to a solution of *N,N*-dialkylhydroxybenzamide ligand (2 equiv.) in dichloromethane (5 mL) at 25°C. The solution instantaneously became yellow. After stirring for 1 h, the volatiles were removed under reduced pressure and the resulting solid residue was redissolved in dichloromethane. This sequence was repeated three times to ensure the complete removal of isopropanol. The resulting crude solid was recrystallized by layering a dichloromethane solution of the compound with hexanes at -35°C.

Preparation of 6a. Compound **6a** was prepared from **5a** (341.9 mg, 1.54 mmol) and titanium isopropoxide (219.6 mg, 0.772 mmol) by following the general procedure for preparation of titanium complexes. Pale yellow crystals of **6a** were obtained in 69% yield (297.0 mg). X-ray-quality crystals were grown from a dichloromethane solution of **6a** layered with hexanes at -35°C. ¹H NMR (360 MHz, CDCl₃) δ 7.21 (td, *J* = 1.5 Hz, *J* = 7.6 Hz, 2H), 7.03 (dd, *J* = 1.5 Hz, *J* = 7.8 Hz, 2H), 6.83 (d, *J* = 8.3 Hz, 2H), 6.52 (t, *J* = 7.2 Hz, 2H), 5.05 (sept, *J* = 6.0 Hz, 2H), 4.8 - 2.7 (br m, 4H), 1.27 (d, *J* = 6.2 Hz, 12H), 1.12 (br s, 24H) ppm; ¹³C{¹H} NMR (90 MHz, CDCl₃) δ 172.9, 167.6, 132.5, 127.4, 121.4, 120.6, 115.2, 77.4, 54 - 45 (br), 25.7, 21.1 ppm; IR (KBr film) 2966, 2930, 2865, 2226, 1601, 1570, 1535, 1469 cm⁻¹.

Preparation of 6b. Compound **6b** was prepared from **5b** (217.2 mg, 0.751 mmol) and titanium isopropoxide (106.7 mg, 0.375 mmol) by following the general procedure for preparation of titanium complexes. Pale yellow crystals were obtained in 92% yield (255.4 mg). X-ray-quality crystals were grown from a dichloromethane solution of **6b** layered with hexanes at -35°C. ¹H NMR (360 MHz, CDCl₃) δ 7.22 (t, *J* = 7.8 Hz, 2H), 7.14 (m, 12H), 6.88 (dd, *J* = 1.5 Hz, *J* = 7.8 Hz, 2H), 6.73 (br s, 8H), 6.57 (d, *J* = 8.2 Hz, 2H), 6.35 (t, *J* = 7.6 Hz, 2H), 4.53 (sept, *J* = 6.1 Hz, 2H), 0.98 (d, *J* = 6.2 Hz, 12H) ppm; ¹³C{¹H} NMR (90 MHz,

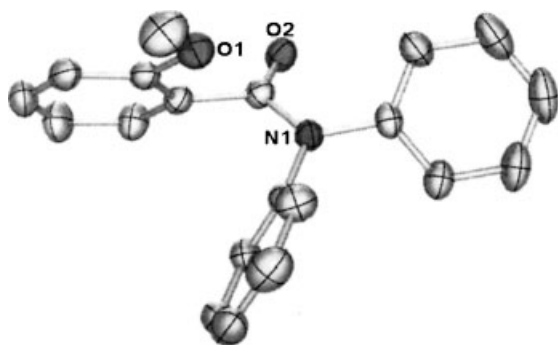


Fig. 2. Structure of **4b**. The carbonyl C-O bond length is 1.220(2) Å and the torsional angle between the aryl ring and the amide is 114.9(16)°.

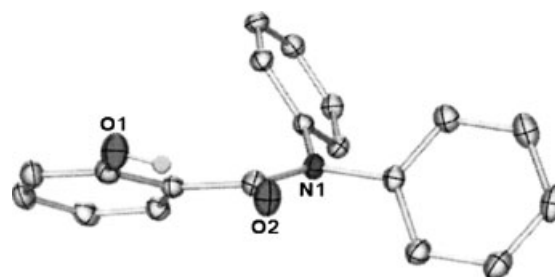


Fig. 3. Structure of **5b**. The carbonyl C-O bond length is 1.241(2) Å and the torsional angle between the aryl ring and the amide is 27.5(3)°.

CDCl₃) δ 172.4, 168.5, 144.4, 134.0, 130.8, 129.3, 127.4, 126.5, 121.7, 118.1, 115.2, 77.6, 24.9 ppm; IR (KBr film) 2966, 2954; 2944; 1616, 1606, 1575, 1565, 1545, 1535, 1489, 1464, 1443, 1372 cm⁻¹.

RESULTS AND DISCUSSION

The vast majority of atropisomeric compounds used in asymmetric synthesis are derived from biaryls. Examples that have been extraordinarily successful are BINOL,¹²⁻¹⁶ BINAP,^{12,17,18} and their derivatives. In contrast, the use of non-biaryl atropisomeric ligands in asymmetric catalysis is in its infancy.¹⁹⁻²² Recently, chiral atropisomeric amides have been successfully employed as chiral auxiliaries in asymmetric synthesis^{19,23-44} by Curran et al.,^{26,27,45} Simpkins and co-workers,⁴²⁻⁴⁴ Taguchi and co-workers,⁴⁶⁻⁴⁸ and Clayden et al.,^{23,32} among others. We have recently reported the first successful catalytic kinetic resolution of these compounds.⁴⁹

Atropisomeric benzamides where the benzamide group is flanked by two *ortho* substituents exhibit hindered rotation about the Ar-CO(NR₂) bond.^{19,49} The barriers are dependent on the nature of the substituents, as exemplified by compounds **1-3**, which are shown in Figure 1 with their reported half-lives to racemization.¹⁹ Because our

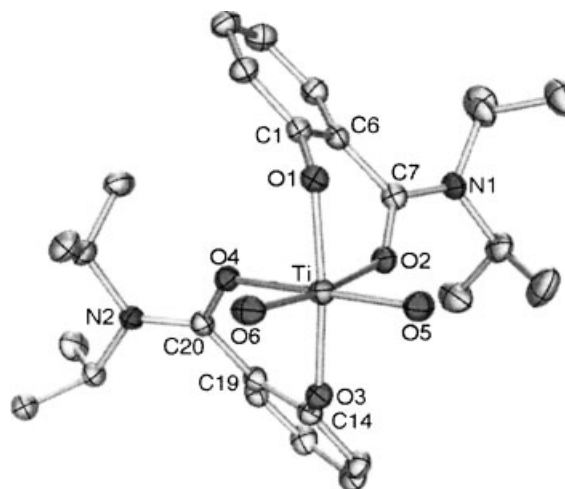
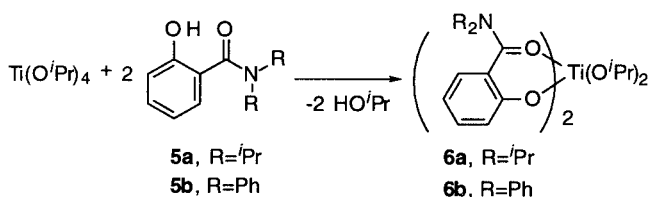


Fig. 4. ORTEP drawing of **6a**. Ellipsoids are at the 30% probability level. Selected bond distances and bond angles are listed in Table 1. The isopropyl groups have been removed from O5 and O6 for clarity. The C1-C6-C7-O2 and C14-C19-C20-O4 torsional angles are 37.0(5)° and 37.3(4)°, respectively.

Scheme 2. Synthesis of **6a** and **6b**.

goal was to design ligands that easily racemize, we chose benzamide derivatives flanked by a single *ortho* substituent. To ensure tight bonding to metals, chelating ligands were desired. Given these guidelines, we examined *ortho*-hydroxybenzamides **5a** and **5b** in Scheme 1.

Ligands **5a** and **5b** were easily prepared from anisic acid (Scheme 1) by reaction with thionyl chloride followed by treatment of the resulting acid chloride with diisopropyl or diphenyl amine to give **4a** and **4b**. Deprotection of **4a** and **4b** was easily accomplished with boron tribromide (71–86% yield).

An important parameter in the enantioselectivity of catalysts bearing BINOL, BINAP, or related ligands is the angle between the naphthyl rings.^{50,51} With this in mind, comparison of the solid state structures of ligand precursor **4b** and ligand **5b** was undertaken to determine the dihedral angle between the aryl ring and the amide group.⁵² Compounds **4b** and **5b** were crystallized from dichloromethane. The structures of **4b** and **5b** were determined at low temperature and ORTEP diagrams are shown in Figures 2 and 3, respectively. Selected bond distances and bond angles are given in the figure captions and data collection parameters are provided in Table 3.

In the structure of **4b**, the dihedral angle between the planes defined by the amide group and the aromatic ring is 114.9(16)° with the amide C–O bond tilted away from the methoxy substituent on the aryl ring. In contrast, in the structure of **5b** the carbonyl group is tilted toward the hydroxyl group and the dihedral angle is 27.5(3)°. The smaller torsional angle in **5b** is due to an intramolecular

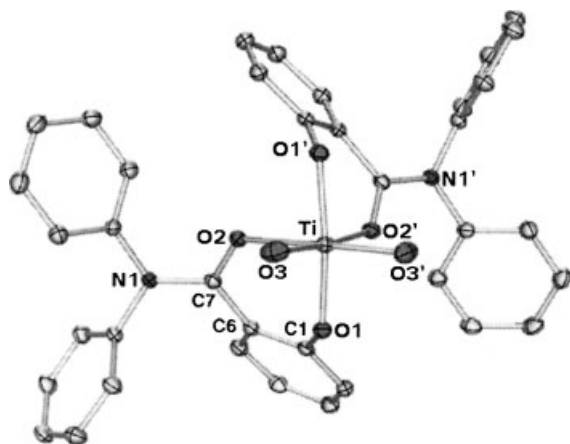


Fig. 5. ORTEP drawing of **6b**. Ellipsoids are at the 30% probability level. Selected bond distances and bond angles are listed in Table 2. The isopropyl groups have been removed from O3 and O3' for clarity. The C1–C6–C7–O2 torsional angle is 34.4(3)°.

TABLE 1. Selected bond distances (Å), angles (°), and torsional angles for **6a**

6a	
Ti–O1	1.924 (2)
Ti–O2	2.157 (2)
Ti–O3	1.931 (2)
Ti–O4	2.142 (2)
Ti–O5	1.819 (2)
Ti–O6	1.823 (2)
C7–O2	1.261 (4)
C20–O4	1.267 (3)
O1–Ti–O2	81.38 (9)
O1–Ti–O3	16.96 (0)
O1–Ti–O4	84.65 (8)
O1–Ti–O5	97.88 (9)
O1–Ti–O6	92.95 (10)
O2–Ti–O3	87.11 (9)
O2–Ti–O4	79.85 (8)
O2–Ti–O5	90.50 (9)
O2–Ti–O6	169.21 (9)
O3–Ti–O4	80.97 (8)
O3–Ti–O5	94.73 (9)
O3–Ti–O6	96.26 (10)
O4–Ti–O5	169.57 (10)
O4–Ti–O6	90.54 (10)
O5–Ti–O6	99.40 (10)
C1–C6–C7–O2	37.05 (43)
C14–C19–C20–O4	37.03 (42)

hydrogen bond between the hydroxyl group and the amide carbonyl oxygen. The O···H distance is 1.906(2) Å. The amide carbonyl C–O bond distance in **5b** of 1.241(2) Å is slightly lengthened with respect to the C–O bond distance in **4b** of 1.220(2) Å. This observation is consistent with an intramolecular hydrogen bond to the carbonyl group in **5b**, which decreases the C–O bond order.

Comparison of the solution spectra of **4a** and **5a** also suggests an interaction between the OH and C=O groups in **5a**. The ¹H NMR spectrum of **4a** contains two inequivalent resonances for the isopropyl methylenes and four doublets (two of which partially overlap) for the isopropyl

TABLE 2. Selected bond distances (Å), angles (°), and torsional angles for **6b**

6b	
Ti–O1	1.9177 (14)
Ti–O2	2.178 (2)
Ti–O3	1.801 (2)
C7–O2	1.247 (3)
O1–Ti–O1'	157.92 (7)
O1–Ti–O2	81.39 (6)
O1–Ti–O2'	82.22 (5)
O1–Ti–O3	94.72 (6)
O1–Ti–O3'	99.76 (6)
O2–Ti–O2'	83.84 (6)
O2–Ti–O3	172.48 (7)
O2–Ti–O3'	89.27 (7)
O3–Ti–O3'	97.77 (9)
C1–C6–C7–O2	34.4 (3)

TABLE 3. X-ray crystallographic data for **4b**, **5b**, **6a**, and **6b**

	4b	5b	6a	6b
Formula	C ₂₀ H ₁₇ NO ₂	C ₁₉ H ₁₅ NO ₂	TiC ₃₄ H ₅₂ N ₂ O ₆ Cl ₆	TiC ₄₄ H ₄₂ N ₂ O ₆
fw	303.35	289.32	845.38	742.70
Space group	P1̄ (#2)	Pbca (#61)	C2/c (#15)	C2/c (#15)
<i>a</i> , Å	9.5319 (6)	18.5315 (3)	24.7349 (6)	16.5013 (4)
<i>b</i> , Å	10.8004 (6)	17.4426 (2)	10.4409 (2)	9.6975 (2)
<i>c</i> , Å	9.1639 (5)	9.0161 (1)	19.0238 (4)	23.5662 (6)
α, deg	105.308 (4)			
β, deg	99.758 (3)		118.78 (1)	102.047 (1)
γ, deg	110.403 (4)			
<i>V</i> , Å ³	816.38 (8)	2914.34 (7)	4306.6 (2)	3688.0 (2)
<i>Z</i>	2	8	4	4
ρ _{calcd} , g cm ⁻³	1.234	1.319	1.304	1.338
μ(Mo Kα), cm ⁻¹	0.80	0.86	6.12	2.85
R ^a	0.0693	0.0513	0.0763	0.0480
R _w ^b	0.1502	0.1178	0.1743	0.1141

methyl groups. Likewise, the ¹³C{¹H} NMR spectrum of **4a** indicates the inequivalency of the isopropyl groups with four signals for the isopropyl methyl groups and two resonances for the methyne carbons. In contrast, **5a** exhibits a single resonance for the methyne hydrogens and a doublet for all 12 isopropyl methyl hydrogens in the ¹H NMR spectrum, indicating that rotations about the aryl-CO and C-N bonds are fast on the NMR time scale. Likewise, two upfield singlets in the ¹³C{¹H} NMR spectrum, one for the methyl groups and one for the methyne hydrogens, were observed. These data suggest that the rotation about the aryl-amide linkage is facilitated by the hydrogen bond in **5a**.

The IR data for the ligand precursors **4a** and **4b** are similar, with the CO stretching frequencies at 1619 and 1652 cm⁻¹, respectively. As anticipated, the CO stretches for the deprotected amides **5a** and **5b** are at lower frequency (1582 and 1631 cm⁻¹, respectively).

Reaction of 2 equiv. of ligands **5a** and **5b** with titanium tetraisopropoxide readily proceeded to give L₂Ti(O^{*i*}Pr)₂ and two equiv. of isopropanol (Scheme 2). These compounds were crystallized by layering hexanes on dichloromethane solutions of the compounds. The ORTEP diagrams of **6a** and **6b** are shown in Figures 4 and 5, respectively.⁵² Bond distances and angles are given in Tables 1 and 2 for compounds **6a** and **6b**, respectively. Data collection parameters for both structures are listed in Table 3.

Both structures are monomeric L₂Ti(O^{*i*}Pr)₂ complexes and contain distorted octahedral titanium centers. The amide ligands are bidentate, bound to titanium through both the aryloxy oxygen and the amide carbonyl oxygen. In each case, the phenoxy oxygens are *trans* and the isopropoxy groups are *cis*. In the structure of **6b**, the titanium lies on a crystallographically imposed C₂-symmetry axis, while **6a** is approximately C₂-symmetric. The torsional angles between the aromatic ring and the amide for compounds **6a** and **6b** are similar, ranging from 34.4° to 37.3°. The torsional angle between the amide and aryloxy groups of **6a** are more easily seen in Figure 6, where the substituents have been removed from the oxygens.

The C=O distances in **6a** are 1.261(4) Å and 1.267(3) Å,

while that for **6b** is 1.247(3) Å. The C=O distance in **6b** is slightly longer than that of the unbound ligand **5b** and the ligand precursor **4b**. The titanium isopropoxide Ti-O bond distances fall between 1.801(2) Å and 1.823(2) Å and are within the expected range.⁵³

The titanium phenoxide Ti-O distances in **6a** and **6b** are between 1.917(1) Å and 1.931(2) Å, which are longer than titanium phenoxide distances in four-coordinate complexes of the type (ArO)₂TiX₂ (1.7 Å to 1.8 Å).^{54–56} The titanium phenoxide Ti-O distances in **6a** and **6b** are longer than the terminal Ti-O distances in the octahedral dimeric [Ti(OPh)₄(HOPh)]₂ (1.789–1.884 Å),⁵⁷ octahedral titanium salen complexes (salen)TiX₂ (X=Me, Cl, OAr), which range from 1.829 Å to 1.899 Å,^{58–60} and (tetrahydrosalen) Ti(O-*i*Pr)₂ (1.905 Å to 1.914 Å).⁶¹ The titanium amide carbonyl Ti-O bond distances are considerably longer, as expected, and range from 2.142(2) Å to 2.178(2) Å. The titanium complexes each exhibit two C=O stretches at 1601 and 1570 cm⁻¹ for **6a** and 1616 and 1606 cm⁻¹ for **6b**.

The ¹H NMR spectra of **6a** and **6b** are informative in that they both contain doublets for the Ti(O-*i*Pr)₂ isopropoxy methyl groups. In the static structure of the C₂-symmetric complexes, the isopropoxy methyl groups are diastereotopic and inequivalent. However, the ¹H NMR spectra indicate that these groups are equivalent on the NMR time scale. The interconversion of the enantiomeric

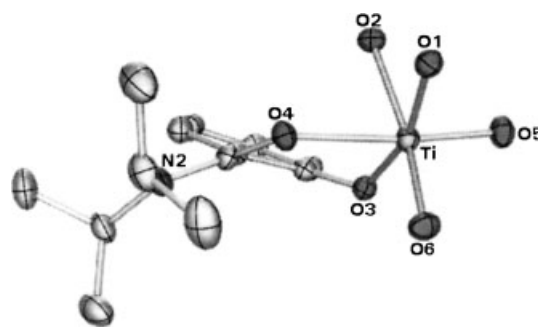


Fig. 6. A view of the dihedral angle between the aryloxy group and the amide in **6a**.

conformations of the bound ligand can be envisaged to take place by dissociation of the amide carbonyl from the titanium, bond rotation, and recapture of the carbonyl oxygen. This process will also scramble the stereochemistry at the titanium center. Inversion of configuration of both amide ligands alone is not sufficient to result in equilibration of the isopropoxy methyl groups, because it does not invert the stereochemistry at the titanium center. This action would give rise to a diastereomer. A possibility that is unlikely, but cannot be ruled out, is a rapid intermolecular alkoxide exchange process.

In summary, we have designed ligands that are bidentate and we have shown that they have chiral conformations. The next phase of this research involves the application of these ligands to asymmetric catalysis.

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