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# Enantiopure Pseudo-$C_3$-Symmetric Titanium Alkoxide with Propeller-Like Chirality

**Philip Axe,[†] Steven D. Bull,*[,†] Matthew G. Davidson,*[,†] Carly J. Gilfillan,[†] Matthew D. Jones,[†] Diane E. J. E. Robinson,[†] Luke E. Turner,[†] and William L. Mitchell[‡]**

*Department of Chemistry, University of Bath, Claverton Down, Bath, BA2 7AY, U.K., and Neurology Medicinal Chemistry 3, GSK PLC, Harlow, Essex, CM19 5AW, U.K.*

*s.d.bull@bath.ac.uk; m.g.davidson@bath.ac.uk*

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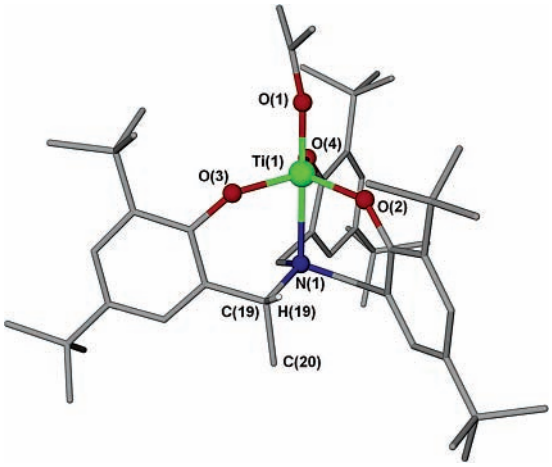
## ABSTRACT




**An enantiopure amine tris(phenolate) ligand containing a single stereogenic center has been used to control the propeller-like chirality of a derived pseudo-$C_3$-symmetric titanium isopropoxide complex with excellent levels of diastereocontrol.**

Tripodal trianionic ligands such as triamido amines[1] and trialkoxy amines[2,3] have been used extensively for stabilizing unusual metal coordination geometries and as scaffolds for catalytically active metal complexes. Recently, amine tris(phenolate) ligands **1a**,**b** have been introduced as a new class of tripodal ligand for fundamental coordination studies and as supports for metal-based catalysts (Figure 1).[4] These ligands are particularly well-suited to catalytic applications because they generally afford well-defined monomeric metal complexes that are stable to hydrolysis,[5] while retaining useful catalytic activity.[6,7] Significantly, for the purposes of this study, a number of these metal complexes display helical chirality, with $C_3$-symmetric Ti(IV) alkoxide complexes demonstrating unusually high barriers to racemization.[8] All reports to date have employed achiral amine tris(phenolate)

[†] University of Bath.
[‡] GSK PLC.

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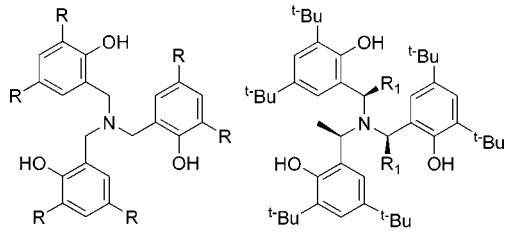


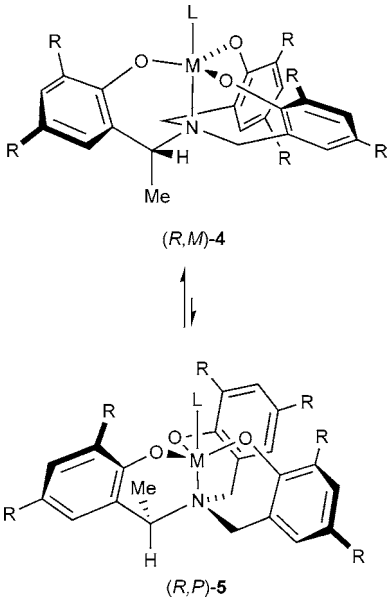
**1a** (R = Me)
**1b** (R = $^t$Bu)

(*R*,*R*,*R*)-**2** ($R_1$ = Me)
(*R*)-**3** ($R_1$ = H)

**Figure 1.** Ligands **1a**,**b**, (*R*,*R*,*R*)-**2**, and (*R*)-**3**.

ligands for the synthesis of racemic metal complexes, with potential applications of enantiopure metal complexes remaining unexplored. We reasoned that a pseudo-$C_3$-symmetric ligand such as (*R*)-**3** might be useful for the preparation of chiral metal complexes with potential applications for chiral recognition or asymmetric catalysis.[9] Consequently, we now report herein on the synthesis and structural characterization of a chiral pseudo-$C_3$-symmetric titanium alkoxide (*R*,*M*)-**12** that employs a chiral relay strategy[10] to control the propeller-like chirality of its amine tris(phenolate) ligand.

Although the potential of using $C_3$-symmetric ligands for the preparation of chiral metal complexes for asymmetric catalysis has been recognized, there are only a limited number of chiral $C_3$-symmetric metal complexes currently



(*R*,*M*)-**4**

(*R*,*P*)-**5**

**Figure 2.** (*R*,*M*)-**4** and (*R*,*P*)-**5** diastereoisomers of a five-coordinate metal complex of tetradentate ligand (*R*)-**3**.

available.[9,11,12] Although a chiral $C_3$-symmetric version of amine tris(phenolate) ligand (*R*,*R*,*R*)-**2** may be envisaged, the presence of three benzylic stereocenters means that it is difficult to prepare in enantiopure form without recourse to multistep synthesis as has been found previously for other $C_3$-symmetric ligand systems.[13] Consequently, we considered an alternative ligand design for controlling the propeller-like chirality of metal complexes derived from a chiral, tetradentate ligand (*R*)-**3** that contains a single stereogenic center.

It was proposed that complexation of the amine tris(phenolate) to a five-coordinate metal center would result in a chiral metal complex (*R*,*M*)-**4** whose helical chirality would be controlled by its stereogenic α-methyl group adopting a pseudoaxial conformation. This diastereoisomer would occur preferentially because formation of the corresponding diastereoisomer (*R*,*P*)-**5** would be disfavored by *syn*-pentane-like interactions between the pseudoequatorial α-methyl group and its proximal aryl ring (Figure 2). Although examples of this type of conformational control are rare, precedent does exist for control of helical chirality using point chirality within metal−ligand complexes.[14,15]

The enantiomerically pure ligand (*R*)-**3** was prepared in six steps using the synthetic protocol described in Scheme 1. 2-(Benzyloxy)-3,5-di-*tert*-butyl-benzaldehyde **6** was re-

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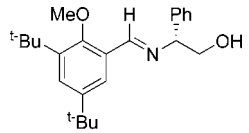
(16) The configuration of the newly formed stereocenter of amine (*R*,*R*)-**8** was assigned as (*R*) from an established literature precedent for addition of methyllithium to this class of chiral imine and subsequently confirmed from analysis of the X-ray crystal structure of (*R*,*M*)-**12**. See: Bernardinelli, G.; Fernandez, D.; Gosmini, R.; Meier, P.; Ripa, A.; Schupfer, P.; Treptow, B.; Kundig, E. P. *Chirality* **2000**, *12*, 529.
(17) A similarly poor yield was obtained for addition of methyllithium to the structurally related imine (*R*)-**13** under these conditions. See: Kundig, E. P.; Botuha, C.; Lemercier, G.; Romanens, P.; Saudan, L.; Thibault, S. *Helv. Chim. Acta* **2004**, *87*, 561.



(*R*)-**13**

(18) The configuration and enantiomeric purity of amine (*R*)-**9** was confirmed as >95% ee using our recently published NMR chiral derivatization protocol involving treatment with 2-formyl-phenylboronic acid and enantiopure BINOL. See: Pérez-Fuertes, Y.; Kelly, A. M.; Johnson, A. L.; Arimori, S.; Bull, S. D.; James, T. D. *Org. Lett.* **2006**, *8*, 609.
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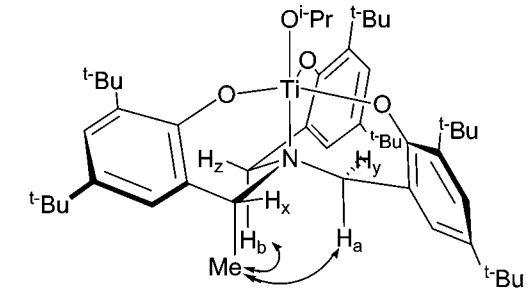


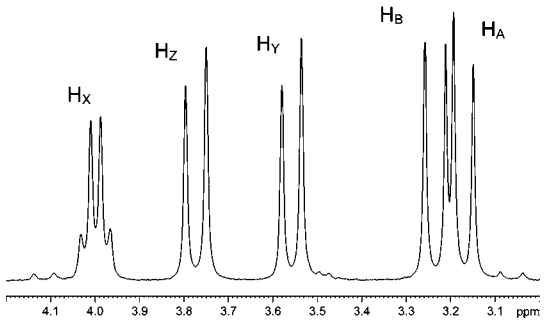




**Figure 3.** Selected NOEs and benzylic region of the $^1$H NMR spectrum of (*R*,*M*)-**12**.

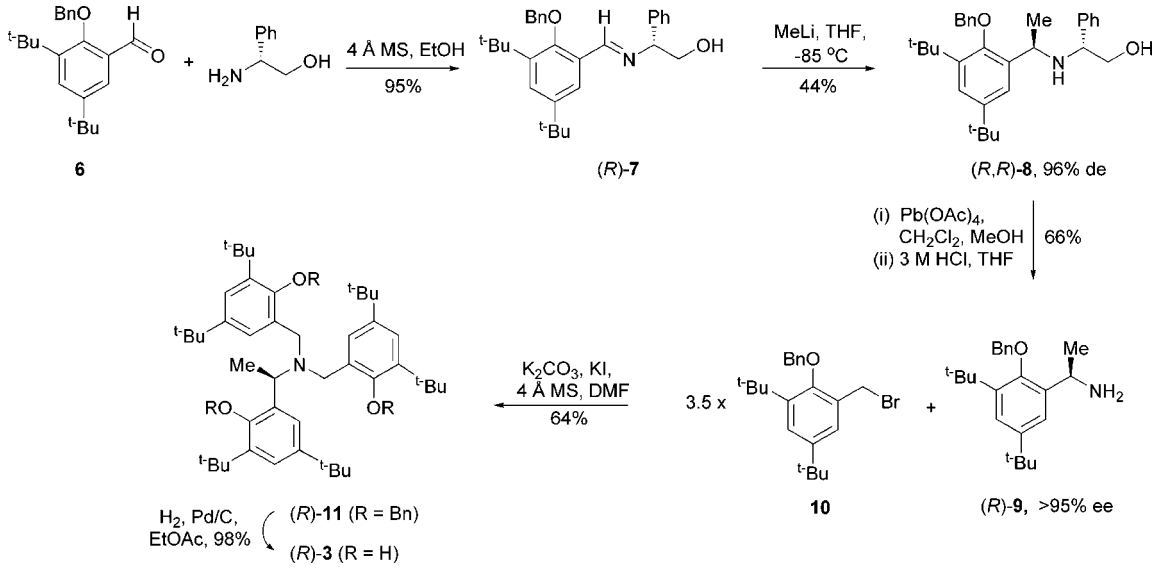
acted with (*R*)-phenylglycinol to afford chiral imine (*R*)-**7** in 95% yield. Nucleophilic addition of methyllithium to imine (*R*)-**7** in THF at −85 °C gave chiral amine (*R*,*R*)-**8** in 44% yield and 96% de.[16,17] Deprotection of this secondary amine (*R*,*R*)-**8** was achieved via a two-step protocol involving oxidative cleavage with $Pb(OAc)_4$, followed by acidic hydrolysis using 3 M $HCl_{(aq)}$, to afford primary amine (*R*)-**9** in 66% yield and >95% ee.[18] Primary amine (*R*)-**9** was then bisbenzylated with 2-(benzyloxy)-1-(bromo-methyl)-3,5-di-*tert*-butyl-benzene **10** in the presence of KI under basic conditions to afford tertiary amine (*R*)-**11**. Subsequent hydrogenolytic deprotection of the benzylic groups of (*R*)-**11** gave the desired ligand (*R*)-**3** in 63% yield over the two steps.[19]

Reaction of ligand (*R*)-**3** with titanium tetra(isopropoxide) gave an analytically pure yellow solid (*R*,*M*)-**12** in 65% yield. $^1$H NMR spectroscopic analysis of (*R*,*M*)-**12** indicated that the proposed chiral relay strategy was successful in controlling the propeller-like conformation of the ligand. The $^1$H NMR spectrum of (*R*,*M*)-**12** revealed a quartet and four AB doublets (two partially overlapped) between $\delta$ 4.05 and $\delta$ 3.10, corresponding to the two pseudoaxial and three pseudoequatorial benzylic protons ($J_{gem} \geq 13.0$ Hz) of the ligand fragment (Figure 3). A NOE experiment established close proximity between the α-methyl protons and the two inequivalent pseudoaxial benzylic protons. This observation is consistent *only* with the predicted pseudoaxial orientation of the α-methyl group implying that the complex exists in solution as (*R*,*M*)-**12** (Figure 3).

An X-ray crystal structure of (*R*,*M*)-**12** was obtained (Figure 4a) which is consistent with the structure inferred in solution by NMR spectroscopy.[20] Key structural parameters within (*R*,*M*)-**12** are similar to those observed previously for racemic titanium complexes derived from ligand **1a**.[6] The approximately trigonal bipyramidal titanium center lies slightly above the plane of the three equatorial phenolate oxygen atoms, and the axial sites are occupied by the neutral nitrogen atom of the ligand and the monodentate isopropoxide anion.

The absolute (*R*)-configuration of the pseudoaxial α-methyl stereocenter locks the helical chirality of the aryl substituents of the chiral ligand into a (*M*)-propeller conformer. The average tilt of the aryl groups (as defined by the average angle between the aryloxide planes and the Ti−N bond

**Scheme 1.** Asymmetric Synthesis of Chiral Amine (*R*)-**3**



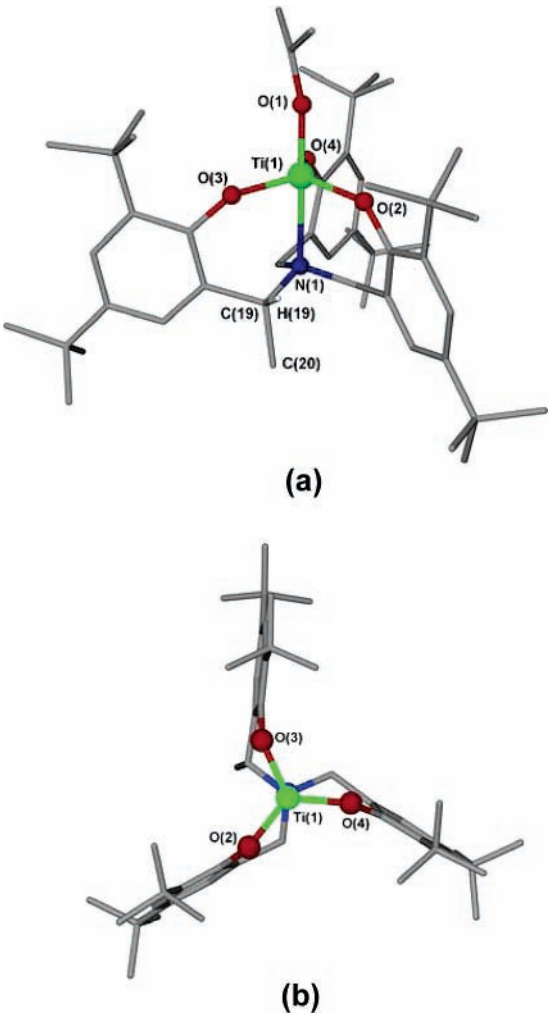



**Figure 4.** Molecular structure of (*R*,*M*)-**12**. (a) View highlighting the pseudoaxial α-methyl stereocenter (carbon framework shown in outline only, and hydrogen atoms except H19 omitted for clarity). (b) View highlighting the propeller-like conformation of the complex (isopropoxide ligand omitted for clarity). Selected bond lengths (Å) and angles (deg): Ti(1)−O(1) 1.786(2), Ti(1)−O(2) 1.848(2), Ti(1)−O(3) 1.836(2), Ti(1)−O(4) 1.848(2), Ti(1)−N(1) 2.351(2), N(1)−Ti(1)−O(1) 179.51(9), O(3)−Ti(1)−O(2) 116.35(1).

vector) is 11°. Viewing the structure of (*R*,*M*)-**12** along the Ti−N bond vector from the top face reveals that the three proximal *t*-butyl groups serve to create a $C_3$-symmetric environment within the coordination sphere of the titanium atom (Figure 4b). This strongly suggests that monomeric transition-metal complexes derived from (*R*)-**3** that are used for stereocontrol should behave in a manner identical to thecorresponding metal complexes derived from "true" $C_3$-symmetric ligands such as (*R*,*R*,*R*)-**2**.

In conclusion, incorporation of a single stereogenic center into an amine (trisphenolate) ligand (*R*)-**3** controls the propeller-like conformation of the ligand on coordination to a five-coordinate metal center. We have shown that the titanium alkoxide complex (*R*,*M*)-**12** possesses pseudo-$C_3$-symmetry both in solution and in the solid state. Unlike racemic complexes derived from achiral ligands, inversion does not occur in solution, even at elevated temperatures, suggesting that the α-methyl group imparts a high degree of control over helical chirality. Therefore, to the best of our knowledge, this represents the first example of an enantiomerically pure and conformationally stable metal phenolate complex. We are currently investigating whether the helical chirality of metal complexes derived from pseudo-$C_3$-symmetric ligand (*R*)-**3** can be exploited for chiral recognition[21] or asymmetric catalysis.[22]

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**Supporting Information Available:** Experimental details and spectroscopic characterization for these compounds together with the crystal data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) **Crystal data:** $C_{55}H_{89}NO_4Ti$, $M$ = 876.17, yellow prism, 0.40 × 0.30 × 0.25 mm$^3$, tetragonal, space group $P4_3$, $a = b$ = 14.584(2), $c$ = 25.374(4) Å, $V$ = 5396.87(13) Å$^3$, $Z$ = 4, $D_c$ = 1.078 g/cm$^3$, $F_{000}$ = 1920, Mo Kα radiation, $\lambda$ = 0.71073 Å, $T$ = 150(2) K, $2\theta_{max}$ = 55.0°, 21 199 reflections collected, 11 331 unique ($R_{int}$ = 0.0279). Final GOF = 1.024, R1 = 0.0560, wR2 = 0.1464, $R$ indices based on 9438 reflections with $I > 2\sigma(I)$ (refinement on $F^2$), 573 parameters, 1 restraint, $\mu$ = 0.200 mm$^{-1}$. Absolute structure parameter = 0.02(3). All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were calculated at idealized positions and refined using the riding model. The largest peak and hole in the final difference Fourier map were 0.53 and −0.37 Å$^{-3}$. Crystallographic data have been deposited at the Cambridge Crystallographic Data Centre with reference number CCDC 623640. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif.

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