Enantiopure Ti(IV) Amino Triphenolate Complexes as NMR Chiral Solvating Agents

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ABSTRACT Enantiopure Ti(IV) complexes bearing pseudo-C_3 amino triphenolate ligands have been synthesized and characterized. The complexes bearing ortho phenyl groups act as ^{1}H NMR chiral solvating agent (CSA) for the stereochemical analysis of a series of sulfoxides. The coordination of a Lewis base coligand (sulfoxide) and the presence of aromatic rings are the key structural factors for the efficiency of the CSA. *Chirality 23:796–800, 2011.*

KEY WORDS: titanium complexes; triphenolamine; sulfoxides; chiral solvating agents

INTRODUCTION

Triphenolamines have recently emerged as an important class of ligands, which form stable metal complexes able to perform effectively in catalysis.[1] In particular, d^0 metal complexes have shown to be effective catalysts in polymerizations,[2,3] oxygen transfer processes,[4–7] and Diels–Alder reactions.[8,9] Ti(IV) complexes, based on solution nuclear magnetic resonance (NMR) data and X-ray crystallography, form as racemic mixtures of Δ and Λ species, resulting from a helical wrapping of the ligand around the metal ion, with racemization barriers of $\Delta G^{\ddagger}$ = 65.7–74.4 kJ/mol. Control of the handedness of the complex helicity can be obtained introducing a single, remote stereocenter at one of the benzylic position. Recently, this approach has been used by Bull and Davidson[10,11] and by us [Fig. 1 (*R*)-**1a**].[12] Enantiopure complexes were obtained as single diastereoisomers in solution and as well as in the crystal structure. Because of the high catalytic performances of their racemic analogs, the properties of the enantiopure versions of these complexes have been investigated, but modest stereoselections have been observed.[11] However, we have previously observed that Ti(IV) complexes can coordinate an extra basic ligand, such as sulfoxides;[13,14] therefore, we decided to investigate the ability of enantiopure Ti(IV) amino triphenolate complexes to coordinate chiral sulfoxides and eventually discriminate the two enantiomers, thus performing as chiral solvating agents (CSAs). Although enantiopure sulfoxides are important class of chiral molecules,[15] a limited number of effective CSAs for this class of molecules are available.[16,17] Pirkle's alcohol, (*S*) or (*R*)-1-(9-anthryl)-2,2,2,-trifluoroethanol,[18] and Kagan's CSA, (*R*)-(3,5-dinitrobenzoyl)-α-methyl benzyl amine,[19] are usually used, and they have been found to be effective also with rather complex sulfinylic derivatives.[20,21] Other systems based on 2-arylpropionic acids and related structures have been reported as well.[22]

EXPERIMENTAL

Materials and Methods

General remarks. Dry solvents were purchased from Fluka, where "degassed" solvents or solutions are noted. Degassing was carried out by three freeze-pump-thaw cycles. Chemicals were purchased from Aldrich, Fluka, or Acros and used without further purification. Compounds **2c** and **3c** have been synthesized according to literature.[12] If not mentioned, all reactions were carried out under nitrogen, and the glassware was oven-dried before use. Molecular sieves (3 and 4 Å) were heated (160 °C) under vacuum (0.4 mbar) for 16 h. Flash chromatography: silica gel 60 (40 μm), P.H. Stehlin A. G. T.L.C.: Merck SIL G/UV254; detection by UV/vis or by treatment with Ce–Mo-staining reagent made from $Ce(SO_4)_2$ (4.0 g), $H_3PMo_{12}0_{40}$ (8.0 g), and H_2SO_4 (80.0 g) in 320 ml water. Optical rotations were measured on a PerkinElmer 241 polarimeter, *c* in g/100 ml. Infrared spectroscopy (IR) spectra were recorded on a PerkinElmer fourier transform infrared spectroscopy (FTIR) 1650. ^{1}H and ^{13}C{^{1}H} NMR spectra (referenced to tetramethylsilane or residual solvent peak) were recorded at 301 K on Bruker AC-250, 300, and 400 MHz instruments. MS: electrospray ionization mass spectrometry (ESI-MS) experiments were carried out in positive mode on an Agilent Technologies LC/MSD Trap SL AGILENT instrument, mobile phase acetonitrile/formic acid 0.1–1%. high resolution mass spectrometry (HRMS) (electrospray ionization mass spectrometry-time of flight detector (ESI-TOF)) were performed in an Applied Biosystems ESI-TOF Mariner™ Biospectrometry™ Workstation, acetonitrile/formic acid 0.1% as mobile phase with internal standards. In all cases, isotope patterns were in agreement with the theoretical ones.

(R)-1-(2-Benzyloxyphenyl)ethylamine Hydrochloride (4). (*R*)-2-(1-Aminoethyl)phenol hydrochloride (100 mg, 0.73 mmol, 1.0 equiv) was dissolved in N,N-Dimethylformamide (DMF) (3 ml), followed by Et_3N (103 μl, 0.73 mmol, 1.0 equiv) and Boc_2O (175 mg, 0.80 mmol, 1.1 equiv). The mixture was stirred in N_2 atmosphere overnight. The mixture was then diluted with brine (10 ml) and CH_2Cl_2 (20 ml), and the aqueous layer was extracted with CH_2Cl_2 (2 × 15 ml); the organic phases reunited and dried over Na_2SO_4. Concentration in vacuo yielded a red–brown oil which was dissolved in a mixture of MeOH/$CHCl_3$ (1/2, 2 ml) and added to a previously stirred suspension of K_2CO_3 (444 mg, 3.2 mmol, 4.4 equiv) in MeOH/$CHCl_3$ (1/2, 2 ml; N_2-atmosphere). After the addition of benzyl bromide (105 μl, 0.8 mmol, 1.2 equiv), the resulting suspension was refluxed for 24 h (N_2-atmosphere). The mixture was filtered and concentrated in vacuo. The residue was dissolved in $CHCl_3$

Additional Supporting Information may be found in the online version of this article.

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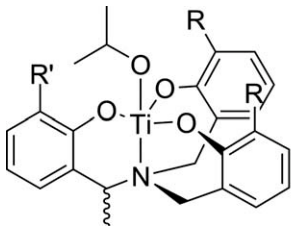


(*R*)-**1a** R = Me, R'=H
(*R*)-**1b** R = *tert*-Bu, R'=H
(*R*)-**1c** R = Ph, R'=H
(*S*)-**1d** R=Ph, R'=Ph

Fig. 1. Titanatranes **1a–d**.

(15 ml), washed with saturated NH_4Cl, dried over Na_2SO_4, and concentrated. The resulting pale-yellow oil was dissolved in 4 M HCl/dioxane (12 ml), and the mixture was stirred for 10 min. This solution was concentrated, and the residue crystallized from toluene/p.e. yielding a light-brown crystalline solid (180 mg, 94%).

M.p.: 195–198 °C. $[\alpha]_D^{20}$: −16.6 (c = 0.5 in EtOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.50 (m, 1H, ArH), 7.43–7.23 (m, 6H, ArH), 6.93–6.87 (m, 2H, ArH), 5.15 ("d"-AB system, 2H, J = 2.3 Hz, CH_2O), 4.81 (quintet, 1H, J = 6.0 Hz, $CHCH_3$), 1.67 (d, 3H, J = 6.8 Hz, $CHCH_3$). ^{13}C NMR (75.5 MHz, CDCl3): δ 154.3, 135.5, 128.6, 127.4, 126.8, 126.1, 126.1, 124.9, 120.1, 110.9, 69.0, 45.5, 17.8 MS (ESI): 228.2 $[M+H]^+$ (calcd. 228.3). Elemental analysis %: experimental (calculated), C, 55.60 (55.34); H, 6.99 (6.97); N, 8.11 (8.07).

2-Benzyloxy-1-bromomethyl-3-methylbenzene (3a). $NaBH_4$ (250 mg, 6.6 mmol, and 1.5 equiv) was added in one portion to a solution of aldehyde **2a** (1.00 g, 4.4 mmol) in 2-propanol (15 ml). The resulting suspension was stirred at r.t. overnight. The mixture was then concentrated in vacuo and dissolved in a mixture of Et_2O (40 ml) and 1 M NaOH (30 ml). The aqueous phase was washed with Et_2O (2 × 25 ml). The combined organic phases were reunited and washed with brine (15 ml). The solution, dried over Na_2SO_4 and concentrated in vacuo, yielded a pale-yellow oil, which was dissolved in dry toluene (20 ml) and placed on ice bath for 5 min under N_2-atmosphere. PBr_3 (1.35 g, 469 μl, 4.8 mmol, and 1.1 equiv) was dissolved in a small amount of toluene (4 ml) and added drop by drop to the solution. The resulting mixture was stirred on ice bath for 20 min and at room temperature for 30 min. The solution was diluted with cold water (20 ml) and toluene (10 ml) and stirred vigorously. The organic phase was separated, washed with saturated aqueous $NaHCO_3$ (10 ml), brine (10 ml), and dried over Na_2SO_4. The resulting solution was concentrated in vacuo yielding a pale-yellow oil (1.07 g, 84%).

^{1}H NMR (250 MHz, $CDCl^3$): δ 7.55–7.03 (m, 8H, ArH), 5.03 (s, 2H, CH2O), 4.58 (s, 2H, CH_2Br), 2.36 (s, 3H, CH_3); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 155.6, 137.3, 132.2, 132.0, 131.5, 129.3, 128.7, 128.3, 128.0, 124.7, 74.8, 28.8, 16.5. Elemental analysis %: experimental (calculated) C, 61.31 (61.87); H, 5.21 (5.19).

2-Benzyloxy-1-bromomethyl-3-tert-butylbenzene (3b). Aldehyde **2b** (10.0 g (85%), 37.3 mmol) was dissolved in 2-propanol (200 ml) and $NaBH_4$ (1.69 g, 44.7 mmol, 1.2 equiv) was added in one portion. The resulting suspension was stirred at r.t. overnight. The mixture was partially concentrated and dissolved in a mixture of Et_2O (200 ml) and 10% KOH (100 ml). The aqueous phase was extracted with Et_2O (100 ml), and the combined organic phases were washed with brine (50 ml), dried over Na_2SO_4, and concentrated. A pale-yellow liquid (9.9 g) was obtained, and it was used directly in the next step. The oil was dissolved in dry toluene (170 ml) and placed on ice bath for 10 min (N_2-atmosphere). PBr_3 (11.1 g (97%), 4 ml, 41.0 mmol, 1.1 equiv) was dissolved in toluene (35 ml) and added drop by drop to the solution of alcohol. The mixture was stirred on ice bath for 20 min, and at room temperature for further 30 min. The solution was diluted with cold water (50 ml) and stirred vigorously for 2 min. The organic phase was separated and washed with saturated aqueous $NaHCO_3$ (100 ml). The aqueous layer was washed with additional toluene (50 ml), and the organic phases were washed with water (70 ml), dried over Na_2SO_4, filtered through a pad of celite, and concentrated yielding a pale-yellow oil (9.0 g, 85%).

1H NMR (250 MHz, $CDCl_3$): δ 7.59–7.06 (m, 8H, ArH), 5.13 (s, 2H, CH_2O), 4.59 (s, 2H, CH_2Br), 1.43 (s, 9H, CH_3C); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 156.7, 143.7, 137.6, 132.1, 130.8, 128.7, 128.2, 128.0, 126.9, 124.5, 75.6, 35.6, 31.3, 29.6; elemental analysis %: experimental (calculated) C, 65.09 (64.87); H, 6.39 (6.35).

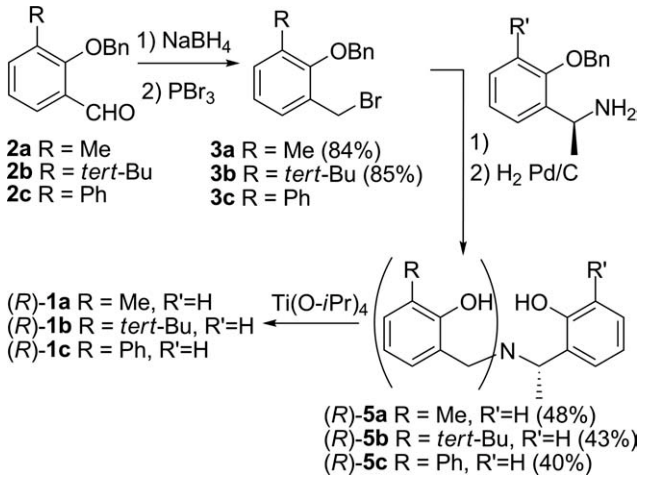
(R)-Bis-(2-hydroxy-3-methylbenzyl)-[1-(2-hydroxyphenyl)ethyl]amine (5a). The starting bromide **3a** (315 mg, 1.1 mmol, 2.2 equiv), amine (*R*)-**4** (130 mg, 0.5 mmol, 1.0 equiv) and K_2CO_3 (340 mg, 2.5 mmol, 5.0 equiv) were dissolved/suspended in dry MeCN (10 ml) and refluxed for 40 h (N_2-atmosphere). The reaction was followed by thin-layer chromatography (TLC) (EA/p.ether = 1/9). The mixture was filtered, the filtration cake washed with additional ethyl acetate (EA), and the combined solutions concentrated [0.37 g, ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.62–6.86 (m, 25H, ArH), 4.96 (s, 2H, CH_2O), 4.63 (s, 4H, CH_2O), 4.57 (q, 1H, J = 7.2 Hz, CH), 3.84 (d, 2H, J = 15.0 Hz, CH_2N), 3.74 (d, 2H, J = 15.0 Hz, CH_2N), 2.24 (s, 6H, $ArCH_3$), 1.34 (d, 3H, J = 7.0 Hz, CH_3)]. The crude protected triphenolamine was dissolved in EA (23 ml) and 10% Pd/C (32 mg) was added. After 2 h, the mixture was filtered through a pad of celite and concentrated, resulting in isolation of a pale-yellow solid. Precipitation from a mixture of CH_2Cl_2/hexane gave a pale-yellow solid (90 mg, 48%).

$[\alpha]_D^{20}$: −99.0 (c = 0.1 in CH_2Cl_2). M.p.: 132–135 °C. IR (KBr): 3398, 3046, 2973, 2921, 1594, 1472, 1387, 1227, 1199, 1083, 843, 749. ^{1}H NMR (250 MHz, $CDCl_3$): δ 9.22 (bs, 3H, OH), 7.28–6.68 (m, 10H, ArH), 4.63 (q, 1H, J = 6.8 Hz, CH), 4.24 (d, 2H, J = 12.8 Hz, CH_2N), 3.52 (d, 2H, J = 12.8 Hz, CH_2N), 2.35 (s, 6H, $ArCH_3$), 1.52 (d, 3H, J = 7.0 Hz, CH_3); ^{13}C NMR (75.5 MHz, CDCl3): δ 156.5, 154.6, 131.2, 129.5, 128.6, 127.7, 125.7, 125.4, 121.3, 119.7, 119.1, 117.1, 53.1, 52.0, 16.3, 8.6 MS (ESI): 378.2 $[M+H]^+$. Elemental analysis %: experimental (calculated) C, 75.99 (76.36); H, 7.20 (7.21); N, 3.74 (3.71).

(R)-Bis-(2-hydroxy-3-tert-butylbenzyl)-[1-(2 hydroxyphenyl)ethyl] amine (5b). The starting bromide **3b** (0.9 g, 2.7 mmol, 2.2 equiv), amine (*R*)-**4** (324 mg, 1.2 mmol, 1.0 equiv) and K_2CO_3 (848 mg, 6.1 mmol, 5.0 equiv) were dissolved/suspended in dry MeCN (15 ml) and refluxed for 48 h (N_2-atmosphere). The reaction is followed by TLC (EA/p.ether = 1/19). The mixture was diluted with EA, filtered, and concentrated. Light-brown oil; used directly in the next step [0.99 g, ^{1}H NMR (300 MHz, CDCl3): δ 7.70 (m, 2H, ArH), 7.42–7.10 (m, 19H, ArH), 7.02 (m, 2H, ArH), 6.89–6.81 (m, 2H, ArH), 4.95 (d, 1H, J = 12.3 Hz, CH_2O), 4.88 (d, 1H, J = 12.3 Hz, CH_2O), 4.70 (s, 4H, CH_2O), 4.37 (q, 1H, J = 6.9 Hz, CH), 3.81 (d, 2H, J = 14.7 Hz, CH_2N), 3.71 (d, 2H, J = 14.7 Hz, CH_2N), 1.36 (s, 18H, CH_3C), 1.23 (d, 3H, J = 6.9 Hz, CH_3CH)]. The protected triphenolamine (2.7 mmol) was dissolved in EA (50 ml), and 10% Pd/C (150 mg) was added. The mixture was stirred under H_2-atmosphere. After 2 h, the solution was filtered through a pad of celite and concentrated, resulting in the isolation of a light-brown foam. Purification by column chromatography (EA/p.ether = 1/30, SilicaGel) led to isolation of white foam (240 mg, 42%).

$[\alpha]_D^{20}$: −77.6 (c = 0.1 in CH_2Cl_2). M.p.: 71–74 °C. IR (KBr): 3429, 2957, 2918, 2871, 1608, 1590, 1482, 1452, 1436, 1359, 1288, 1205, 1083, 846, 747. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.27 (m, 2H, ArH), 6.96–6.66 (m, 8H, ArH), 4.29 (q, 1H, J = 7.0 Hz, CH), 3.71 (d, 2H, J = 13.2 Hz, CH_2N), 3.18 (d, 2H, J = 13.2 Hz, CH_2N), 1.55 (s, 18H, CH_3C), 1.01 (d, 3H, J = 7.2 Hz, CH_3CH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 154.6, 154.5, 137.3, 129.5, 128.9, 128.4, 127.1, 122.6, 120.6, 119.8, 117.0, 52.5, 52.1, 34.8, 29.8, 9.0 (one signal overlapped). MS (ESI): 462.3 $[M+H]^+$. Elemental analysis %: experimental (calculated) C, 77.99 (78.05); H, 8.44 (8.52); N, 3.00 (3.03).

(R)-Bis-(2-hydroxybiphenyl-3-ylmethyl)-[1-(2-hydroxyphenyl)ethyl] amine (5c). The starting bromide **3c** (440 mg, 1.25 mmol, and 2.2 equiv), amine (*R*)-**4** (149 mg, 0.6 mmol, and 1.0 equiv), and K_2CO_3 (391 mg, 2.8 mmol, and 5.0 equiv) were dissolved/suspended in dry MeCN (6 ml) and refluxed for 48 h (N_2-atmosphere). The reaction was followed by TLC (EA/p.ether = 1/9; NMR). The mixture was concentrated, the residue dissolved/suspended in $CHCl_3$ (40 ml) and washed with diluted brine (15 ml), the aqueous layer extracted with $CHCl_3$ (15 ml), the organic phase dried over Na_2SO_4 and concentrated yielding a light-brown viscous oil [510 mg, ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.76 (m, 2H, ArH), 7.56–6.90 (m, 33H, ArH), 4.98 (s, 2H, CH_2O), 4.71 (q, 1H, J = 7.0 Hz, CH), 4.23 (s, 4H, CH_2O), 3.91 (d, 2H, J = 12.8 Hz, CH_2N), 3.82 (d, 2H, J = 12.8 Hz, CH_2N), 1.43 (d, 3H, J = 6.8 Hz, CH_3)]. The crude protected



Scheme 1. Synthesis of enantiopure trifenolamines **5a–c** and their titanatrane complexes **1a–c**.

triphenolamine (400 mg, 0.52 mmol) was dissolved in toluene (20 ml), and 10% Pd/C (50 mg) was added. After 4 h, the reaction was filtered through a pad of celite and concentrated, resulting in the isolation of yellow oil. The product was purified by column chromatography (EA/toluene = 1/15; Silicagel) yielding a pale-yellow oil (120 mg, 40%).

$[\alpha]_D^{20}$: +19.4 (c = 0.1 in CH_2Cl_2). M.p.: 145–148 °C. IR: 3422, 3056, 2972, 2926, 1608, 1590, 1497, 1460, 1431, 1382, 1290, 1222, 1082, 755, 699. ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.40–7.06 (m, 16H, ArH), 6.87–6.77 (m, 4H, ArH), 6.35 (bs, 3H, OH), 4.41 (q, 1H, J = 6.8 Hz, CH), 3.86 (d, 2H, J = 15.6 Hz, CH_2N), 3.81 (d, 2H, J = 15.6 Hz, CH_2N), 1.58 (d, 3H, J = 7.0 Hz, CH_3). ^{13}C NMR (75.5 MHz, CDCl3): δ 156.0, 151.5, 136.9, 130.3, 129.6, 129.0, 128.7 (4 × CH), 128.2, 127.3, 127.1, 123.3, 119.9, 119.2, 116.2, 54.9, 50.2, 9.1. MS (ESI): 502.2 $[M+H]^+$. Elemental analysis %: experimental (calculated) C, 80.99 (81.41); H, 6.22 (6.23); N, 2.77 (2.79).

General Procedure for Preparation of Titanium Complexes

Ligands **5a–c** were dissolved in deuterated chloroform in a 1-ml volumetric flask. In the same way, a stock solution of Ti(O-*i*Pr)$_4$ was prepared (2-ml volumetric flask). Afterward, solutions corresponding to equimolar amounts of reagents were mixed in a 1-ml volumetric flask and more solvent was added up to 1 ml. The resulting solution was transferred to a screw-cap NMR tube and formation of the complex was monitored via ^{1}H NMR.

(5R)-1-Iso-propoxytitana-2,10,11-trioxa-6-AZA-5-methyl-3,4-benzo-8,9;12,13-bis(6′-methylbenzo)[4.4.4.01,6]tricyclotetradecane (1a). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.24–6.69 (m, 10H, ArH), 5.20 (septet, 1H, J = 6.0 Hz, CHO), 3.76 (d, 1H, J = 13.5 Hz, CH_2N), 3.57 (d, 1H, J = 13.5 Hz, CH_2N), 3.25 (d, 1H, J = 13.5 Hz, CH_2N), 3.21 (d, 1H, J = 13.5 Hz, CH_2N), 2.29 (s, 3H, CH_3Ar), 2.26 (s, 3H, CH_3Ar), 1.55 (d, 3H, J = 6.0 Hz, CH_3CHO), 1.54 (d, 3H, J = 6.3 Hz, CH_3CHO), 1.51 (d, 3H, J = 6.9 Hz, CH_3CHN); signal CHN overlapped by *i*-PrOH (4.02 ppm); HR-MS (ESI): calcd for $C_{25}H_{28}NO_4Ti$: 454.1495, found 454.1484.

(5R)-1-Iso-propoxytitana-2,10,11-trioxa-6-aza-5-methyl-3,4-benzo-8,9;12,13-bis(6′-tert-butylbenzo)[4.4.4.01,6]tricyclotetradecane (1b). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26–6.72 (m, 10H, ArH), 5.21 (septet, 1H, J = 6.0 Hz, CHO), 3.70 (d, 1H, J = 14.1 Hz, CH_2N), 3.56 (d, 1H, J = 13.2 Hz, CH_2N), 3.21 (d, 2H, J = 12.6 Hz, CH_2N), 1.52 (d, 6H, J = 5.7 Hz, CH_3CHO), 1.46 (s, 9H, CH_3C), 1.44 (s, 9H, CH_3C); signal CHN overlapped by i-PrOH (4.01 ppm), signal CH_3CHN overlapped by apical i-PrOH (1.52 ppm); ^{13}C NMR (75.5 MHz, $CDCl_3$): 163.7, 163.1, 162.7 (Ar-O), 136.5, 128.7, 128.4, 128.2, 127.9, 127.5, 126.3, 125.2, 125.1, 120.7, 120.4, 120.2, 116.5, 80.4, 77.5, 64.7, 54.0, 53.2, 51.2, 35.0, 29.8, 26.0, 25.6, 9.1. HR-MS (ESI): calcd for $C_{31}H_{40}NO_4Ti$: 538.2435, found 538.2458.

(5R)-1-Iso-propoxytitana-2,10,11-trioxa-6-AZA-5-methyl-3,4-benzo-8,9;12,13-bis(6′-phenylbenzo)[4.4.4.01,6]tricyclotetradecane (1c). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.67–7.63 (m, 4H, ArH), 7.42–7.06 (m, 12H, ArH), 6.95–6.87 (m, 3H, ArH), 6.77 (m, 1H, ArH), 4.78 (septet, 1H, J = 6.0 Hz, CHO), 4.14 (q, 1H, J = 6.6 Hz, CHN), 3.89 (d, 1H, J = 14.1 Hz, CH_2N), 3.66 (d, 1H, J = 13.2 Hz, CH_2N), 3.36 ("t", 2H, J = 15.0 Hz, CH_2N), 1.59 (d, 3H, J = 6.9 Hz, CH_3CHN), 1.18 (d, 3H, J = 6.0 Hz, CH_3CHO), 1.16 (d, 3H, J = 6.3 Hz, CH_3CHO); ^{13}C NMR (75.5 MHz, $CDCl_3$): 159.4, 159.0, 158.6, 140.4, 140.1, 130.6, 130.4, 130.3, 130.0, 129.8, 128.9, 128.2, 127.9, 127.5, 125.34, 125.29, 125.0, 122.3, 115.4, 115.3, 112.7, 112.6, 112.5, 80.6, 64.7, 55.4, 25.6, 25.0, 24.8, 21.3, 21.0, 20.9. HR-MS (ESI): calcd for $C_{35}H_{32}NO_4Ti$: 578.1809, found 578.1833.

RESULTS AND DISCUSSION

Three new enantiopure ligands (*R*)-**5a–c** have been prepared according to the protocol described recently for ligand (*S*)-**5d** (Scheme 1).[12] This strategy requires the synthesis of the protected benzyl bromide **3a–c** from the corresponding aldehydes **2a–c**. Two equivalents of benzylbromides **3a–c** react with the chiral amines (*R*)-**4**[23] furnishing the correspondent tertiary amines. Hydrogenolysis using Pd/C as catalyst afforded the desired ligand (*R*)-**5a–c** in satisfactory yields. Triphenolamines (*R*)-**5a–c** cleanly react with Ti(O*i*-Pr)$_4$ in dry $CDCl_3$ yielding the corresponding mononuclear complexes (*R*)-**1a–c** as single diastereomeric species, as confirmed by the ^{1}H NMR spectra. Titanatrane (*S*)-**1d** has been prepared as previously reported.[12]

Chiral complexes **1a–d** have been tested as catalysts in the stereoselective sulfoxidation of *p*-tolyl methyl sulfide furnishing high yields in the sulfoxide but low ees, results in line with what was recently reported by Bull and Davidson for a similar complex (see Supporting Information). However, even if the results, in term of stereoselections, are not appealing, interestingly in the reaction mixture obtained using (*R*)-**1c** and (*S*)-**1d** as catalysts, we notice that the ^{1}H NMR signals corresponding to the methyl group of sulfoxides **7** appeared splitted (Fig. 2). A possible explanation could be that the Ti(IV) complex was acting both as catalyst for sulfoxide forma-

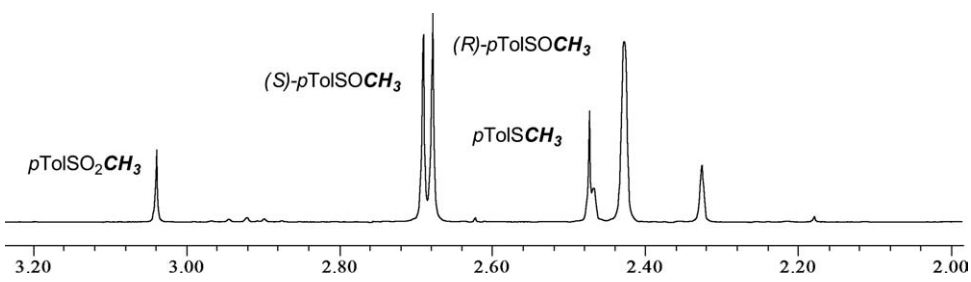


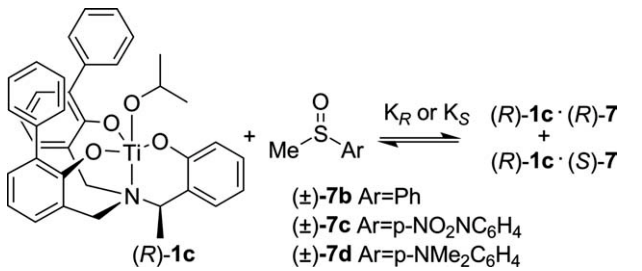
Fig. 2. ^{1}H NMR of the reaction mixture for pTolSMe **6a** oxidation catalyzed by (R)-**1c.**

tion and as CSA for the newly formed sulfoxide. A separation of about 0.1 ppm was observed in a 0.08 M solution of sulfoxide **7a** with 10% of complex (R)-**1c** (Fig. 2).

Addition of commercially available (+)-(*R*)-**7a** resulted into an increasing of the more shielded ^{1}H NMR signal (2.68 ppm) and allowed the assignment, the resonances for the two diastereomeric complexes (*R*)-**1c**·(*S*)-**7a** and (*R*)-**1c**·(*R*)-**7a,** respectively. These preliminary results lead us to investigate more in detail this phenomenon. In fact, not only among the large range of CSA used only few are reported for the enantiomeric excess determination of chiral sulfoxides, but also a very limited number of CSA are based on early transition.[17,24] The behavior of the three Ti(IV) complexes (*R*)-**1a–c** in the presence of increasing amount of (±)-methyl phenyl sulfoxide **7b** in $CDCl_3$ has been investigated more in detail and only in the case of complex (*R*)-**1c** a splitting of the methyl signal could be observed. The CSA capability of (*R*)-**1c** has been experimentally evaluated with a series of sulfoxides and other molecules containing a basic donor function. A shift of proton resonances were observed in all the cases but only with aryl methyl sulfoxides a significative splitting on at least one signal was obtained. To gain more detailed information on the process, the binding constants (K_R and K_S) for aryl-methyl sulfoxides with different electronic demand (phenyl, *p*-dimethylamino, and *p*-nitro benzene) (±)-**7b–d** in deuterochloroform were determined via ^{1}H NMR titrations [Table 1; On purpose written routine using Scientist (MicroMath Scientific Software) were used to fit signals for a 1:1 complex].

Titration experiments highlight that the efficient separation originates from two cooperative phenomena: (i) a significant difference in the two coordination constants (the more favorable coordination of complex (*R*)-**1c** with the *R* enantiomers) and (ii) a difference in the chemical shifts induced by complexation (Δδ). Noteworthy, *R* sulfoxides bound twice stronger than the corresponding *S* enantiomers in all cases. This effect combines with larger chemical shift changes observed for the diasteromeric (*R*)-**1c**•(*R*)-**7b–d** complexes. Moreover, in the set of molecules under study, K_a values follow Hammet σ parameter for the substitution of the aromatic ring suggesting an interaction in which the oxygen of the sulfoxide is directly coordinated to the Ti(IV) metal (coordination ability parallels the Lewis basicity of the sulfoxides **7d** > **7b** > **7c**). Indeed, several d^0 metals, such as Ti(IV), V(V), Mo(VI), and Re(VII) have shown the capability to expand their coordination sphere in the presence of an extra ligand.[13,25,26] A confirmation of the mode of binding of the sulfoxide comes from theoretical calculations. The structure of the metal complex (*R*)-**1c** have been optimized using density functional (B3LYP) calculations at the LANL2DZ level (see Supporting Information).[27] Complex (*R*)-**1c** displays a bipyramidal geometry in agreement with the crystallographic data reported by Bull and Davidson.[10] The coordination with the two enantiomers of sulfoxide **7b** give rise to the formation of two diasteroisomers in which the oxygen is coordinated to the metal.

TABLE 1. Binding constants (K_R/K_S) and Δδ (ppm) of S-CH_3 resonances for sulfoxides 7b–d/(*R*)-1c in $CDCl_3$ at 300 K



Entries	Sulfoxide	K_a (M^{-1})	Δδ (ppm)[a]
1	(*R*)-**7b**	483	−0.12
2	(*S*)-**7b**	213	−0.10
3	(*R*)-**7c**	299	−0.12
4	(*S*)-**7c**	162	−0.09
5	(*R*)-**7d**	675	−012
6	(*S*)-**7d**	337	−0.09

[a]Chemical shifts variation of the S-CH_3 of **7b–d.**

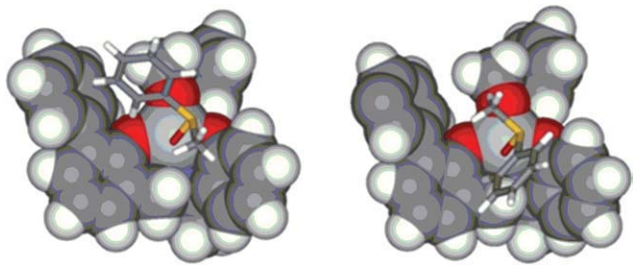


Fig. 3. Minimized structures of diasteromeric complexes (R)-**1c** with (R)-**7b** (left) and (S)-**7b** (right). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

The coordination results in a variation to an octahedrical geometry (Fig. 3). Because of the pseudo-C_3 symmetry of the complex, the coordination of the sulfoxides to each of the three different equatorial sectors affords three different diastereomeric complexes. The geometries of the six diastereomers have been minimized and, in agreement with the experimental results, the diasteromeric complexes formed by (*R*)-**1c** and sulfoxide (*R*)-**7** are more stable (average energy difference = 1 kJ/mol, see Supporting Information). This is probably due by additive aromatic stabilizing interactions between the phenyl moieties present on the upper rim of the complex and the aromatic ring of the sulfoxide (Fig. 3, structure on the left). The methyl group is forced to the center of the aromatic shielding region of complex (*R*)-**1c** explaining the higher variation in chemical shifts observed.[28] The key role of π–π interactions is confirmed when an aliphatic sulfoxide was used. In the case of racemic *n*-octyl methyl sulfoxide, large variations of chemical shifts were observed (around 0.6 ppm) without any significant signal splitting.

CONCLUSIONS

In summary, we developed an efficient methodology for the synthesis of enantiopure amino triphenolate ligands. The corresponding Ti(IV) complexes form as single diastereomers in solution, and they are effective, even if not stereoselective, catalyst for sulfoxidations. Furthermore, they act as CSA for the definition of the stereochemistry and enantiopurity of methyl aryl sulfoxides. Binding constant values and theoretical calculations confirm the high tendency of d^0 metal complexes to expand their coordination sphere for the accommodation of an extra ligand. Moreover, this example

reinforces the idea the C_3 receptors are able to perform as enantiodiscriminating agents.[29–31]

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