Modification of Chiral Dimethyl Tartrate Through Transesterification: Immobilization on POSS and Enantioselectivity Reversal in Sharpless Asymmetric Epoxidation

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ABSTRACT Modification of dimethyl tartrate has been investigated through transesterification with aminoalcohols to provide reactive functionalities for the covalent bonding of chiral tartrate to polyhedral oligomeric silsesquioxanes. The transesterification of dimethyl tartrate has been widely studied using different catalytic systems and reaction conditions. Through the proper selection of both the catalytic system and the reaction conditions, it is possible to achieve monosubstituted or bis-substituted tartrate derivatives as sole products. All the intermediate chiral tartrate-derived ligands were successfully used in the homogeneous enantioselective epoxidation of allylic alcohols providing moderate enantiomeric excess over the products. Attached amine groups have been used to support the modified tartrate ligands on to a haloaryl-functionalized silsesquioxane moiety. This final chiral tartrate ligand displays reverse enantioselectivity in the asymmetric epoxidation of allylic alcohols with regard to the starting dimethyl tartrate ligand, both molecules having the same chiral sign. However, the POSS-containing ligand can be easily recovered in almost quantitative yield and reused in asymmetric epoxidation reactions. In addition, recovered silsesquioxane-pendant ligand, though displaying decreasing catalytic activity in recycling epoxidation tests, showed very stable enantioselective behavior. Chirality 22:675-683, 2010. © 2009 Wiley-Liss, Inc.

KEY WORDS: tartrate ligands; transesterification; asymmetric epoxidation; enantioselectivity reversal; POSS

INTRODUCTION

The development of the titanium-tartrate system as a chiral catalyst for the asymmetric epoxidation of allylic alcohols (the sharpless asymmetric epoxidation) has been one of the major breakthrough in enantioselective synthesis,¹⁻³ as revealed by the large number of publications related to this topic (the topic 'Sharpless asymmetric epoxidation' gives 581 entries in a search performed on Sci-Finder Scholar). Thus, the asymmetric epoxidation of allylic alcohols has become a valuable tool for the synthesis of enantiopure epoxy-alcohols, which are versatile chiral building blocks.^{4,5} However, one of the main drawbacks of this process is the complexity of the work-up procedure for carrying out the oxidation and quenching the reaction. Thus, not only are large amounts of solvents necessary to purify the products but also the reuse or recovery of the catalyst becomes impossible. Different attempts, more or less successful, have been carried out to overcome these problems. Some of these deal with the possibility of supporting the chiral ligands on different solids, both organic or inorganic, to obtain heterogeneous analogs to the Sharpless homogeneous catalyst.^{6–9} In this way the quenching of the reaction is largely simplified, since the filtration of the catalysts is enough to stop the reaction and also the catalyst is reusable. However, the immobiliza-© 2009 Wiley-Liss, Inc.

tion of the catalytic species leads, in most of the cases, to a great decrease in the catalytic activity because mass transfer becomes a limiting stage of the reaction process. An interesting way to prepare reusable catalysts without introducing mass transfer restrictions consists of using a carrier for the catalytic active species which helps the recovering of the catalytic complex. One of the possibilities deals with the handling of polyhedral oligomeric silsesquioxanes (POSS) which easily dissolve or precipitate depending on the organic solvent, allowing their recovering. Silsesquioxanes are organosilicon compounds usually employed as models for the study of the behaviour of certain species immobilized on to the surface of silica-based supports. Those compounds have been applied to the immobilization of both metal species¹⁰⁻¹² or organic compounds,13,14 giving an approximate idea of the catalytic behaviour of the grafted species on to the surface of solid supports. However, operating with these species simplifies the working procedures since, through the proper choice

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Scheme 1. Enantioselective synthesis of mono 3 and di-amine 4 esters from dimethyl tartrate 1.

of the solvent, silsesquioxanes can disolve to form homogeneous catalytic systems but they are easily recovered by selective precipitation in other solvents, such as THF.

The work described here presents the modification of chiral tartrate molecules, starting from dimethyl L-(+)-tartrate 1, suitable for covalent bonding to properly functionalized silsesquioxanes. This approach is based on the modification of the ester groups, which minimizes the structural change with respect to catalyst enantioselectivity (Scheme 1). The enantiopure tartrate-derived ligands were used, together with titanium isopropoxide, in the asymmetric epoxidation of various allylic alcohols, using tert-butyl hydroperoxide (TBHP) as oxidant agent, providing good asymmetric induction. Silsesquioxane-pendant tartrate ligands showed reversal enantioselective with regards nonmodified tartrate in the epoxidation of cinnamyl alcohol, being this result attributed to the bulky size of the silicon substituent. Recycling tests with POSSfunctionalized tartrate ligands showed constant enantioselectivity though the activity decreases in reutilization runs.

EXPERIMENTAL Materials and General Procedures

Dimethyl-L-tartrate (DMT, Acros, +99%) and N-methyl ethanolamine (NMEA, Aldrich, 99%) were distilled under an inert atmosphere before being used. *N*-butyl tin hydroxide oxide (Aldrich, 97%) was used as received. Titanium chloride was used and stored in dry box. TBHP anhidrous solution in dichloromethane was prepared from acqueous solution (TBHP, Aldrich, 70%) by extraction with dichloromethane followed by azeotropic distillation in a dean-stark for solvents heavier than water. The obtained solution was characterized by iodometric titration and stored at low temperature (+4°C) in presence of activated 3Å molecular sieves.

All nonaqueous reactions were carried out under an inert atmosphere (usually nitrogen or argon) using standard Schlenk techniques, avoiding at all times the presence of traces of water in the starting materials. Solvents were distilled before use as follows: CHCl₃ from P₂O₅; THF from Na/benzophenone; benzene and toluene from Na. Melting points were determined using a Mettler Toledo DSC822e. NMR spectra were recorded on a Varian Mercury 400 MHz spectrometer. Chemical shifts are reported *Chirality* DOI 10.1002/chir

in parts per million (ppm), in reference to the residual proton signals from the deuterated solvents. FTIR analysis were acquired on a Mattson Infinity series FTIR spectrometer using the KBr buffer technique. Elemental analyzes were performed on a Elementar Vario EL III. Thin layer chromatography (TLC) was carried out using precoated sheets (Aldrich silica gel) and visualizing the products by developing with phosphomolybdic acid/ethanol or ammonium molybdate and cerric sulfate in H_2SO_4/H_2O .¹⁵ Product purification was carried out, unless otherwise stated, on a semipreparative scale Varian Prepstar HPLC fitted with a normal phase Dynamax Microsorb 100–8 Si column (250 mm length, 41.4 mm I.D.) using n-hexane:i-propanol mixtures as solvent.

Protection of Starting Materials

tert-Butyl 2-hydroxyethyl(methyl)carbamate (5). To a solution of 2 (10 g, 0.133 mol) in THF (50 ml) at 0°C, was added a solution of di-*tert*-butyl dicarbonate (32 g, 0.146 mol) in THF (10 ml) dropwise. The reaction mixture was stirred overnight at room temperature and then concentrated in vacuo. The residue was purified by semipreparative HPLC to give the title compound (21.5 g, 0.123 mol, 92%). ¹H NMR (400 MHz, CDCl₃): $\delta = 1.36$ (s, 9H; $-C(CH_3)_3$), 2.82 (s, 3H; $-N-CH_3$), 3.25 (m, 2H; $-N-CH_2-$); 3.61 ppm (m, 2H; $-CH_2-OH$). ¹³C NMR (100 MHz, CDCl₃): $\delta = 28.2$ ($-C(CH_3)_3$), 34.9 ($-N-CH_3$), 51.3 ($-CH_2-OH$), 60.8 ($-N-CH_2-$), 79.5 ($-C(CH_3)_3$), 156.7 ppm ($-N-CO_2-tBu$). IR v_{max} (neat): 1682 (C=O), 2975 (C-H), 3435 cm⁻¹ (O-H). Elemental analysis calcd (%) for $C_8H_{17}NO_3$: C 54.84, H 9.78, N, 7.99; found: C 54.81, H 9.77, N 8.03.

Dimethyl (2R, 3R, 5R', 6R') 5,6-dimethoxy-5,6-dimethyl-1,4-dioxane-2,3-dicarboxylate (6). To a solution of **1** (10.0 g, 55.6 mmol), trimethylorthoformate (TMOF, 17.8 g, 166.9 mmol) and 2,3-butanodione (6.0 g, 67.6 mmol) in methanol, was added camphorsulfonic acid (CSA, 1.3 g, 54.8 mmol). The mixture was then heated under reflux and stirring was continued overnight. The reaction was quenched by slow addition of NaHCO₃ (10 g, 119 mmol) and reflux was maintained for two more hours. The resultant suspension was filtered and concentrated to dryness, giving a brown solid. The residue was then purified by recrystallization from n-hexane/ethyl acetate to give the desired product as a white solid (14.3 g, 49,0 mmol, 88.1%). m.p. 105.2°C. ¹H NMR (400 MHz, CDCl₃): δ = 1.34 (s, 6H; $-C-CH_3$), 3.30 (m, 6H; $-O-CH_3$), 3.75 (s, 6H; $-CO_2CH_3$), 4.51 ppm (m, 2H; -O-CH-). ¹³C NMR (100 MHz, CDCl₃): $\delta = 17.4$ (-C-CH₃), 48.5 $(-O-CH_3)$, 52.5 $(-CO_2CH_3)$, 68.7 (-O-CH-), 99.0 (C-CH₃), 168.1 ppm (-CO₂CH₃). IR v_{max} (KBr): 1030, 1141, 1204, 1756 (C=O), 2956 (C-H) cm⁻¹. Elemental analysis calcd (%) for C₁₂H₂₀O₈: C 49.31, H 6.90; found: C 49.47, H 6.94.

Dimethyl (4R,5R) 2-phenyl-1,3-dioxolane-4,5dicarboxylate (7). A solution of 1 (10.0 g, 55.6 mmol) was mixed with benzaldehyde dimethyl acetal (9.4 g, 61.1 mmol) in benzene (50 ml). To this mixture was added ptoluenesulfonic acid (0.05 g, 0.3 mmol) in a 100 ml round

bottom flask connected to a Dean-Stark apparatus for solvents lighter than water. The mixture was heated under reflux for 12 h during which time the solvent was withdrawn from the Dean-Stark trap in order to displace the equilibrium. The reaction was allowed to cool and then quenched with K_2CO_3 (4.2 g, 30.0 mmol). The resultant suspension was filtered and concentrated in vacuo to give a yellowish solid. The residue was recrystallized from CH_2Cl_2/n -hexane to give compound 7 (13.1 g, 49 mmol, 89%). m.p. 73.2°C. ¹H NMR (400 MHz, CDCl₃): $\delta = 3.84$ (s, 3H; -CO₂CH₃), 3.89 (s, 3H; -CO₂CH₃), 4.92 (d, 2H, J = 4.0Hz; -O-CH-), 6.15 (s, 1H; -CH-Ph); 7.47 ppm (5H; HAr). ¹³C NMR (100 MHz, CDCl₃): d = 52.9 $(-CO_2CH_3)$, 76.7 (-O-CH-), 106.6 (CH-Ph), 127.0, 128.2 and 129,9 (HCAr), 135.0 (CAr), 169.8 (-CO₂CH₃). IR υ_{max} (KBr): 1108, 1244, 1435, 1754 (C=O), 2958 (C-H) cm⁻¹. Elemental analysis calcd (%) for C₁₃H₁₄O₆: C 58.65, H 5.30; found: C 58.40, H 5.37.

Preparation of transesterification catalyst: (2-Methyl-boc-amino)ethyl orthotitanate (8). To a solution of TiCl₄ (0.10 g, 0.53 mmol) in CHCl₃ (10 ml), was added **5** (0.37 g, 2.1 mmol) dropwise to give a yellowish solution. The resultant mixture was then stirred for 30 min and then triethylamine (0.21 g, 2.1 mmol) was added via syringe, giving a colorless suspension. The reaction was then stirred for an additional hour before being used as catalyst for transesterification reactions without further purification.

Transesterification Products

Transesterification reactions were carried out by mixing acetal proctected DMT, **6** or **7** (3.5 mmol scale), and compound **5** (3.5 mmol for monosubstitution reactions, 7.7 mmol for disubstitution reactions) in dry solvents (200 ml), typically benzene. To the resultant mixtures were added the transesterification catalysts: compound **8** (0.53 mmol) and butylstannonic acid (1.7 mmol) for the monosubtitution and disubtitution reactions respectively. The so-prepared suspensions were then heated at reflux for 1 to 3 days, then filtered off through a column of Florisil to remove the organometallic species and concentrated in vacuo. The residues were purified by semi-preparative scale HPLC and the fractions were collected for the main products. In each case the resultant fractions were concentrated in vacuo to give the following products:

2{2-[(*tert*-Butoxycarbonyl)(methyl)amino]ethyl}-3methyl (2*R*,3*R*) 5,6-dimethoxy 5,6-dimethyl-1,4dioxane-2,3-dicarboxylate (9). Compound obtained as a colorless oil (1.43 g, 3.2 mmol, 93%) starting from 6. ¹H NMR (400 MHz, CDCl₃): d = 1.33 (s, 6H; $-C-CH_3$), 1.44 (s, 9H; $-C(CH_3)_3$), 2.90 (s, 3H; CH₃-N-), 3.30 (s, 6H; $-O-CH_3$), 3.45 (m, 2H; $-N-CH_2-$), 3.74 (s, 3H; $-CO_2CH_3$), 4.24 (m, 2H; $-CH_2-O-$), 4.50 ppm (m, 2H; -CH-O-). ¹³C NMR (100 MHz, CDCl₃): d = 17.5($-C-CH_3$), 28.7 ($-C(CH_3)_3$), 35.5 ($-N-CH_3$), 47.3 ($-N-CH_2-$), 48.4 ($-O-CH_3$), 52.4 ($-CO_2CH_3$), 64.2 ($-CH_2-O-$), 68.7 (-CH-O-), 80.0 ($-C(CH_3)_3$), 99.2 ($-C-CH_3$), 154.9 ($-N-CO_2$ tBu), 167.9 ppm ($-CO_2-R$). IR v_{max} (neat): 1043, 1153, 1394, 1459, 1700, 1749, 2959 cm⁻¹. Elemental analysis calcd (%) for $C_{19}H_{33}NO_{10}$: C 52.40, H 7.64, N 3.22; found: C 51.96, H 7.52, N 3.35.

Bis{2-[(*tert*-butoxycarbonyl)(methyl)amino]ethyl} (2*R*,3*R*)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxane-2,3-dicarboxylate (10). This compound was obtained as a colorless oil (2.00 g, 3.47 mmol, 99%) starting from 6. ¹H NMR (400 MHz, CDCl₃): d = 1.30 (m, 6H; $-C-CH_3$), 1.42 (s, 18H; $-C(CH_3)_3$), 2.91 (s, 6H; CH_3-N-), 3.43 (m, 4H; $-N-CH_2-$), 4.22 (m, 4H; $-CH_2-O-$), 4.47 ppm (2H; -CH-O-). ¹³C NMR (100 MHz, CDCl₃): d = 17.7($-C-CH_3$), 28.6 ($-C(CH_3)_3$), 35.8 ($-N-CH_3$), 48.6 ($-N-CH_2-$), 52.8 ($-O-CH_3$), 64.4 ($-CH_2-O-$), 68.6 (-CH-O-), 80.1 ($-C(CH_3)_3$), 99.4 ($-C-CH_3$), 155.8 ($-N-CO_2$ tBu), 167.9 ppm ($-CO_2-CH_2-$). Elemental analysis calcd (%) for $C_{26}H_{46}N_2O_{12}$: C 53.97, H 8.01, N 4.84; found: C 54.12, H 7.88, N 4.65.

4-{2-[(tert-Butoxycarbonyl)(methyl)amino]ethyl}-5methyl (4R,5R)-2-phenyl-1,3-dioxolane-4,5-dicarboxylate (11). This compound was obtained as a colorless oil (0.72 g, 1.76 mmol, 46.8%) starting from 7. 1 H NMR (400 MHz, CDCl₃): d = 1.41 (m, 9H; $-C(CH_3)_3$), 2.86 (s, 3H; CH_3 -N-), 3.28 (s, 2H; -N- CH_2 -), 3.88 (m, 3H; $-CO_2CH_3$), 4.24 (m, 2H; $-CH_2-O_-$), 4.86 (m, 2H; -CH-O-), 6.07 (s, 1H; -CH-Ph), 7.42 ppm (m, 5H; *H*Ar). 13 C NMR (100 MHz, CDCl₃): d = 28.6 $(-C(CH_3)_3)$, 35.3 $(-N-CH_3)$, 47.4 $(-N-CH_2-)$, 52.8 $(-CO_2CH_3)$, 63.7 $(-CH_2-O_{-})$, 77.7 $(-CH_{-}O_{-})$, 80.1 (-C(CH₃)₃), 98.9 (-CH-Ph), 126.7, 127.6 and 129.2 (HC^{Ar}) , 135.2 (C^{Ar}) , 155.2 $(-N-CO_2tBu)$, 167.9 ppm $(-CO_2R)$. Elemental analysis calcd (%) for $C_{20}H_{27}NO_8$: C 58.67, H 6.65, N 3.42; found: C 58.55, H 6.63, N 3.57.

Bis{2-[(*tert*-butoxycarbonyl)(methyl)amino]ethyl} (*4R*,5*R*)-2-phenyl-1,3-dioxolane-4,5-dicarboxylate (12). This compound was obtained as a colorless oil (1.91 g, 3.46 mmol, 92%) starting from **7**. ¹H NMR (400 MHz, CDCl₃): d = 1.43 (s, 18H; $-C(CH_3)_3$), 2.91 (s, 6H; CH_3-N-), 3.46 (m, 4H; $-N-CH_2-$), 4.30 (m, 4H; $-CH_2-O-$), 4.92 (d, 2H; *J*=17.9Hz, -CH-O-), 6.09 (s, 1H; -CH-Ph), 7.44 ppm (m, 5H; *HAr*). ¹³C NMR (100 MHz, CDCl₃): d = 28.7 ($-C(CH_3)_3$), 35.8 ($-N-CH_3$), 47.8 ($-N-CH_2-$), 64.4 ($-CH_2-O-$), 77.7 (-CH-O-), 80.3 ($-C(CH_3)_3$), 107.0 (-CH-Ph), 127.4, 128.5 and 130.1 (HC^{Ar}), 135.6 (C^{Ar}), 155.3 ($-N-CO_2tBu$), 169.3 ppm ($-CO_2CH_3$). Elemental analysis calcd (%) for $C_{27}H_{40}N_2O_{10}$: C 58.68, H 7.30, N 5.07; found: C 58.32, H 7.78, N 4.98.

Bis{2-[(benzyl)(methyl)amino]ethyl} (2*R*,3*R*)-2,3dihydroxybutanedioate (18). This compound was obtained as a yellowish oil (2.06 g, 3.46 mmol, 92%) starting from **7** and subsequent deprotection with Pd/C in ethanol. The product was purified by flash chromatography on silica with hexane:diethyl ether 50:50 vol. ¹³C NMR (100 MHz, CDCl₃): d = 39.5 ($-N-CH_3$), 54.8 ($-N-CH_2-$), 60.5 ($-N-CH_2-Ph$), 62.1 ($-CH_2-O-$), 74.1 (-CH-O-), 126.7, 128.1 snf 128.6 *Chirality* DOI 10.1002/chir (HC^{Ar}) , 135.6 (C^{Ar}) , 137.7 $(-C^{Ar})$, 169.0 ppm $(-CO_2CH_2-)$. Elemental analysis calcd (%) for $C_{24}H_{32}N_2O_6$: C 64.85, H 7.26, N 6.30; found: C 64.98, H 7.27, N 6.32.

Cleavage of Transesterification Products

After transesterification reactions and with the purpose of using modified tartrates as chiral ligands in the asymmetric epoxidation of cinnamyl alcohol, the protecting groups were removed as follows:

- Benzyl acetal protected transesters were treated with catalytic amounts of Pd/C (10%) in methanol under H₂ atmosphere for at least 24 h. The reactions were carried out until no substrate was detected by TLC and then filtered and concentrated in vacuo.
- ii) The 2,3-butanedione and BOC protecting groups were removed by acid treatment with TFA in CH_2Cl_2 . The reactions were carried out in ultrasonic bath until completion and then concentrated in vacuo. The resultant products were purified by crystallization from MeOH/ CH_2Cl_2 at $-30^{\circ}C$.

1-{2-[(*tert***-Butyoxycarbonyl)(methyl)amino]ethyl} 4-methyl (2***R***,3***R***)-2,3-dihydroxybutanedioate (13). Starting from 11** (1.0g, 2.44 mmol) and using deprotection procedure i), the title product was obtained as a light yellow oil (0.78 g, 2.43 mmol, 99%). ¹H NMR (400 MHz, DMSO-D₃): d = 1.38 (s, 9H; $-C(CH_3)_3$), 2.80 (s, 3H; CH_3-N-), 3.41 (m, 2H; $-N-CH_2-$), 3.64 (s, 3H; $-CO_2CH_3$), 4.15 (2xt, 2H; *J*=4.8Hz, *J*=11.8Hz, *J*=17.4Hz, $-CH_2-O-$), 4.39 ppm (m, 2H; -CH-OH). ¹³C NMR (100 MHz, DMSO-D₃): d = 27.6 ($-C(CH_3)_3$); 33.8 ($-N-CH_3$); 46.7 ($-N-CH_2-$); 51.2 ($-CO_2CH_3$); 62.0 ($-CH_2-O-$); 72.1 (-CH-OH); 78.3 ($-C(CH_3)_3$); 153.8 ($-N-CO_2tBu$); 170.7 ppm ($-CO_2R$). Elemental analysis calcd (%) for C₁₃H₂₃NO₈: C 48.59, H 7.21, N 4.36; found: C 48.77, H 7.23, N 4.42.

Bis{2[(*tert*-butyoxycarbonyl)(methyl)amino]ethyl} (2*R*,3*R*)-2,3-dihydroxybutanedioate (14). Starting from 12 (1.0 g, 1.80 mmol), the title compound was obtained using deprotection method i) (0.82 g, 1.76 mmol, 97.5%). ¹H NMR (400 MHz, DMSO-D₃): d = 1.39 (s, 18H; $-C(CH_3)_3$), 2.84 (s, 6H; CH_3-N-), 3.47 (m, 4H; $-N-CH_2-$), 4.25 (s, 4H; $-CH_2-O-$), 4.50 ppm (s, 2H; -CH-OH). ¹³C NMR (100 MHz, DMSO-D₃): d = 28.2 ($-C(CH_3)_3$), 35.1 ($-N-CH_3$), 47.4 ($-N-CH_2-$), 62.9 ($-CH_2-O-$), 72.0 (-CH-OH), 79.5 ($-C(CH_3)_3$), 155.5 ($-N-CO_2$ tBu), 170.4 ppm ($-CO_2$ CH₃). IR υ_{max} (neat): 1203, 1433, 1463, 1679, 1759, 3030, 3345 cm⁻¹. Elemental analysis calcd (%) for $C_{20}H_{36}N_2O_{10}$: C 51.71, H 7.81, N 6.03; found: C 51.85, H 7.74, N 5.97.

1-Methyl 4-[2-(methylamino)ethyl] (2*R*,3*R*)-2,3dihydroxybutanedioate (3). Starting from 13 (0.583 g; 1.81 mmol), using deprotection method ii) gave compound 3 (0.280g, 1.27 mmol, 70%) as needle-shaped crystals after crystallization from CH₂Cl₂/EtOH. The same compound was produced starting from 9 using procedure iii). m.p. = 123,32°C. ¹H NMR (400 MHz, DMSO-D₃): d = 2.60 (s, 3H; CH_3 —N—), 3.22 (s, 2H; —N— CH_2 —), 3.66 (s, 3H; *Chirality* DOI 10.1002/chir -CO₂CH₃), 4.28 (m, 2H; -CH₂-O-), 4.53 ppm (m, 2H; -CH-OH). ¹³C NMR (100 MHz, DMSO-D₃): d = 32.1(-N-CH₃), 46.2 (-N-CH₂-), 51.2 (-CO₂CH₃), 59.1 (-CH₂-O-), 71.5 (-CH-OH), 170.7 ppm (-CO₂R). IR v_{max} (KBr): 1158, 1253, 1399, 1459, 1694, 1754, 2975, 3470 cm⁻¹. Elemental analysis calcd (%) for C₈H₁₅NO₆: C 43.44, H 6.83, N 6.33; found: C 43.67, H 6.92, N 6.52.

(*R*,*R*) bis[2-(Methylamino)ethyl] tartrate (4). Starting from 14 (0.634 g; 1.36 mmol) using deprotection method ii) gave compound 4 (0.312, 1.18 mmol, 87%) as a solid from CH₂Cl₂/EtOH. The same compound was produced starting from 10 using procedure iii). m.p.= 133.73°C. ¹H NMR (400 MHz, DMSO-D₃): d = 2.61 (s, 6H; CH₃-N-), 3.22 (m, 4H; -N-CH₂-), 4.31 (m, 4H; -CH₂-O-), 4.63 ppm (d, 2H; J = 0.8Hz, -CH-OH). d_C ppm (DMSO-D₆, 100 MHz): 32.4 (-N-CH₃), 46.3 (-N-CH₂-), 59.7 (-CH₂-O-), 72.0 (-CH-OH), 170.4 ppm (-CO₂CH₃-). Elemental analysis calcd (%) for C₁₀H₂₀N₂O₆: C 45.45, H 7.63, N 10.60; found: C 45.31, H 7.70, N 10.67.

Silsesquioxane Derived Molecules

(N-Methyl, methylphenylethyl-POSS)-aminoethanol. 15. A solution of chloromethyl)phenylethyl-POSS (1-[2-[(chloromethyl)phenyl]ethyl]-3,5,7,9,11,13,15-heptacyclopentylpentacyclo[9.5.1.13,9.15,15.17,13]octasiloxane) (1 g, 1 mmol) in dichloromethane was treated with 2 (1,5 eq) and pyridine (0,2 eq). The resultant solution was heated to reflux and stirred for 24 h. After the reaction was complete, the solvent was removed under reduced pressure and the crude reaction was suspended in a small quantity of dichloromethane. The product was then recovered by precipitation in acetonitrile in nearly quantitative yield. ¹H NMR (400 MHz, CDCl₃): $\delta = 0.93$ (m; 2H; $-Si-CH_2-$), 0.96 (m, 7H; -Si-CH), 1.47, 1.57 and 1.73 (m, 56H; $-(CH_2)$ -), 2.33 (s, 3H; CH₃-N-), 2.65 (m; 2H; $-N-CH_2-$), 2.71 (m; 2H; $-CH_2-Ph-$), 3.80 (s, 3H; $-O-CH_3$, 3.83 (m, 2H; $-CH_2-OH$), 3.87 (m, 2H; Ar-CH₂-N-), 7.24 and 7.75 ppm (m, 8H; -CH^{Ar}-). ¹³C NMR (100 MHz, CDCl₃): $\delta = 22.4, 27.2$ (C^{Cp}), 41.1 (CH₃-N-), 49.9 (Si-CH-), 51.5 (-O-CH₃), 57.1 $(-CH_2-OH),$ 57.8 $(-Ph-CH_2-N),$ 61 4 $(-N-CH_2-)$, 126.2, 129.1, 130.2 and 140.4 ppm $(-C^{Ar})$. IR v_{max} (neat): 504, 1115, 1450, 2860, 2950, 3431 cm⁻¹. Elemental analysis calcd (%) for C47H81NO13Si8: C 51.66, H 7.47, N 1.28; found: C 51.51, H 7.52, N 1.25.

16. A solution of **15** (0.750 g, in benzene was treated with 7 (1.0 eq) in the presence of butylstannonic acid (0,05 eq). The resultant suspension was then refluxed for 3 days, using a Dean-Stark apparatus to displace the equilibrium, filtered off through a column of Florisil and the clean solution concentrated in vacuo to give a yellow solid. The crude product was suspended in 5 ml of dichloromethane and 50 ml of acetonitrile were added to precipitate the silsesquioxane products. The title compound was then purified by flash chromatography on silica using *n*-hexane:diethyl ether to give a white product (0,725 g, 0,53 mmol, 76%). ¹H NMR (400 MHz, CDCl₃): $\delta = 0.91$ (m, 2H; $-\text{Si}-CH_2-$), 1.00 (m, 7H; $-\text{Si}-CH_3-$), 2.65 (m; 2H;



Scheme 2. Protection of hydroxyl groups from L-(+)-dimethyl tartrate 1 using either 2,3-butanedione or dimethyl-benzaldehyde as reagents.

-N-CH₂-), 2.68 (m; 2H; -CH₂-Ph-), 3.68 (m, 2H; -CH₂-O-), 3.76 (s, 3H; -O-CH₃), 3.85 (m, 2H; Ar-CH₂-N-), 5.01 (m, 2H; -CH-O-), 6.17 (s, 1H; -CH-Ph), 7.24, 7.43, 7.75 ppm (m, 18H; H-Ar). ¹³C NMR (100 MHz, CDCl₃): $\delta = 22.4$ and 27.2 (C^{Cp}), 40.9 (CH₃-N-), 49.9 (Si-CH-), 51.2 (-O-CH₃), 58.4 (-Ph-CH₂-N), 61.9 (-CH₂-O-), 62.6 (-N-CH₂), 80.1 (-CH-O-), 127.4, 128.5, 130.2, 135.5 and 142.1 (- C^{Ar}), 169.5 ppm (-CO₂). IR ν_{max} (neat): 501, 1112, 1450, 1746, 2868, 2950 cm⁻¹. Elemental analysis calcd (%) for C₅₉H₉₁NO₁₈Si₈: C 53.40, H 6.91, N 1.06; found: C 53.47, H 6.74, N 0.98.

17. The cleavage of the benzilidene acetal group in **16** (0.4 g, 0.36 mmol) was carried out using the above deprotection method i) giving 17 as a white solid after washing with acetonitrile (0,417 g, 0.32 mmol, 89%). ¹H NMR (400 MHz, CDCl₃): $\delta = 0.93$ (m, 2H; -Si-CH₂-), 0.97 (m, 7H; -Si-CH), 1.45, 1.51 and 1.73 (m, 56H; -(CH₂)-), 2.39 (s, 3H; CH3-N-), 2.67 (m; 2H; -N-CH2-), 2.71 (m; 2H; -CH2-Ph-), 3.74 (m, 2H; -CH2-O-), 3.79 (s, 3H; -O-CH3), 3.83 (m, 2H; Ar-CH₂-N-), 4.58 (m, 2H; -CH-OH), 7.21 and 7.43 ppm (m, 8H; *H*-Ar). ¹³C NMR (100 MHz, CDCl₃): $\delta = 22.5$ and 27.2 (C^{Cp}), 41.2 (CH₃-N-), 50.0 (Si-CH-), 51.4 (-O-CH₃), 58.0 (-Ph-CH₂-N), 62.3 (-CH₂-O-), 62.5 (-N-CH₂-), 73.0 (-CH-OH), 127.4, 128.5, 130.5 and 141.9 (-CAr), 170.9 ppm (-CO₂-). IR v_{max} (neat): 501, 1112, 1746, 2868, 2950, 3411 cm⁻¹ ¹. Elemental analysis calcd (%) for C₅₂H₈₇NO₁₈Si₈: C 50.41, H 7.08, N 1.13; found: C 50.29, H 7.04, N 1.19.

General Procedure for the Asymmetric Epoxidation of Allylic Alcohols

For comparison purposes the chiral ligands prepared accordingly to the above mentioned procedures have been used in the asymmetric epoxidation of several allylic alcohols in presence of titanium isopropoxide as the metallic source and tert-butyl hydroperoxide as the oxidant. In a typical assay 1.0 g of 4Å molecular sieves were suspended under an inert atmosphere in 50 ml of dry CH_2Cl_2 before cooling the resultant suspension down to -20° C. The next step consisted of the addition of 42 mg of freshly distilled $Ti(OiPr)_4$ (0.15 mmol), an equimolar ammount of the chiral ligand (0.15 mmol) and 2.15 ml of an anhydrous solution of 120 mmol TBHP in dry CH₂Cl₂. The resultant suspension was then stirred for 1 h before adding the substrate (30 mmol) dropwise over 1 h with a syringe pump. The reaction was then stirred for another additional hour. The resultant epoxides were then recovered and purified by semipreparative HPLC. The isolated products were analyzed either by using a GC, fitted with a chiral capillary column (Chiraldex G-TA; 40 m x 0.25 mm) and a FID detector, or by HPLC using *n*-heptane:isopropanol in a chiral column ((*S*,*S*)-Whelk-01; 25 cm \times 2.5 mm) fitted with a UV diode-array detector.

RESULTS AND DISCUSSION Design and Synthesis of Mono (3) and di-amino (4) Ester

Synthesis optimization. For anchoring purposes on an appropriately functionalized silsesquioxane, *N*-methylethanolamine **2**, was chosen as the amine functionality for carrying out a transesterification reaction. To avoid undesired reactions, the hydroxylamine **2** was BOC protected to afford the carbamate **5** as a colorless oil in 95 % yield.

The starting material dimethyl L-tartrate 1, was first protected as the bisacetal by using 2,3-butanedione, accordingly to the methodology developed by Dixon and coworkers,¹⁶ yielding a white solid of (2,3,5,6)-dimethoxy-5,6-dimethyl-1-dioxane-dimethyl tartrate 6 in 90-95% yield after purification by recrystallization, or by using dimethyl-benzyl acetal, following the Seebach procedure,¹⁷ yielding a white solid of 2,3-O-benzylidene-dimethyl tartrate 7, in 90-95% yield after recrystallization (Scheme 2). In both cases, the chirality of the starting tartrate was maintained. The use of different protecting group strategies was justified because of the different de-protection procedures to be employed. Thus, while the dimethoxy-1-dioxane protecting group in 6 may be removed by acid hydrolysis with trifluoroacetic acid (TFA), the benzylidine acetal in 7 may be removed by hydrogenolysis.

The next step in the tartrate modification protocol consisted of the transesterification of the protected starting materials 6 and 7. In this step both the mono (9 and 11) and disubstituted (10 and 12) compounds can be obtained (Scheme 3). For the synthesis of monosubstituted compounds 9 and 11, the acetals 6 and 7 were reacted with BOC ethanolamine **5** using a titanium alkoxide, following a procedure similar to that described by Dixon et al.¹⁸ N-Methyl-tert-butoxycarbonylethanolamine 5 was treated with titanium tetrachloride in the presence of triethylamine as catalyst to give the corresponding titanium alkoxide, 8, (Scheme 4) to be used as a transesterification catalyst. The synthesis of 8 was targetted bearing in mind that transesterification reactions catalyzed by titanium alkoxides take place by the alkoxide binding to the metallic center with transfer to the ester group 19 (Scheme 4).



Scheme 3. Transesterification of protected dimethyl tartrate 6 and 7 with 5 to give the mono and disubstituted compounds, 9–12.



Scheme 4. Preparation of titanium alkoxide 8 catalytic complex based in protected aminoalcohol 5 and transesterification mechanism.

Table 1 sumarizes the results obtained for the transesterification of 6 and 7 with 5 using 8 as catalyst. The investigated titanium alkoxide to tartrate ratios seem to confirm the high catalytic activity of the titanium alkoxide 8, since better yields for the transesterification products are obtained as the titanium content increases (Table 1, entries 1-4). At this point it is noteworthy that the monosubstituted compound 9 is produced as the unique product with Ti/tartrate ratios of 0.05-0.15 (Table 1, entries 1-3). The influence of the solvent polarity on the product distribution has also been investigated (Table 1, entries 5 and 6). Thus, similar results were found when THF or chloroform were used, while the use of a non-polar solvent such as benzene led to a remarkable increase in the yield of the monoester 9, without detecting any of the diester 10 (Table 1, entry 6). These results suggest a strong influence of the polarity of the solvent on the reaction outcome, as less polar solvents provide higher yields of transesterified product 9.

Comparison between the two differently protected starting tartrates revealed that **7** was more reactive than **6** as evidenced from the shorter transesterification reaction times to achieve similar yields of **9** and **11** + **12**, respectively (Table 1, entries 6–7). Monitoring the reaction media during the transtesterification reactions did not reveal the presence of diester 10 when using 6 as starting material, unlike the protected dimethyl tartrate 7, which gave diester 12 after few hours. This difference in behavior could be probably explained by the smaller number of coordinating OR groups in **7**, making the alkoxide more available. As the above methodology is clearly effective in achieving selective monosubstitution, an alternative procedure was employed to synthesize the disubstituted products **10** and **12**. A strongly acidic catalyst, *n*-butyl-stannonic acid, has been described as an effective catalyst for the transesterification reaction of diesters.²⁰ Bearing in mind the effect of the solvent in the monosubstitution transesterifications, benzene was used as the reaction solvent. These results are detailed in Table 2.

Increasing the molar ratio of **5**:**7** led to higher yields of **12** as the main product (Table 2, entries 1, 2 and 3). Additionally, further improvements in the yield of diesters **10** and **12** were obtained by varying the amount of catalyst. The effect of this parameter was more pronounced than altering the amine/DMT molar ratio. Here, the bis-substituted product **10** or **12** was the sole product when the Ti:substrate ratio is raised to 0.5:1 (Table, 2, entries 5 and 6).

The next step in the procedure was the removal of the protecting groups in 9-12, for which two different approaches were used (Scheme 5). In the first route each group was removed separately. Thus, the benzylidene acetal protecting group in modified tartrates 11 and 12 was first removed by hydrogenation, using the method described by Kocienski.²¹ This procedure gave the corresponding diols 13 and 14 in 95% yield after purification by preparative HPLC. Subsequent cleavage of the BOC protecting group was then carried out by acid hydrolysis with CF₃COOH. This gave the deprotected amine modified tartrates 3 and 4 in 70-85% yield after crystallization. Alternatively, a method similar to that developed by Dixon et al.¹⁸ was used to remove the protecting groups from tartrates 9 and 10. Thus, BOC and dimetoxy acetal deprotection was attempted using CF₃COOH at rt. However, using this procedure only the BOC protecting group was removed. It was found that a second treatment increasing the temperature and reaction time up to 24 h vielded the unprotected tartrate 3 and 4.

Synthesis of silsesquioxane-pendant tartrate ligands. To evaluate the behavior of the tartrate-derived compounds as chiral ligands, a step forward in terms of the synthesis of silsesquioxane immobilized ligands (Scheme 6) has been carried out. Initially the haloarylfunctionalized silsesquioxane was reacted with 2 to give

Entry ^a	Compound	Solvent	Catalyst load ^b	Yield monoester (%)	Yield diester (%)
1	6	CHCl ₃	0.05	9 (16)	10 (-)
2	6	CHCl ₃	0.10	9 (14)	10 (-)
3	6	CHCl ₃	0.15	9 (26)	10 (-)
4	6	CHCl ₃	0.20	9 (59)	10 (15)
5	6	THF	0.15	9 (25)	10 (-)
6	6	Benzene	0.15	9 (93)	10 (-)
$7^{\rm c}$	7	Benzene	0.15	11 (47)	12 (27)
8 ^c	7	Toluene	0.15	11 (34)	12 (11)

TABLE 1. Transesterification results using catalyst 8

^aReactions were performed for 72 h at the solvent boiling point temperature, using an equimolar amount of starting materials. ^bTitanium alkoxide:substrate molar ratio.

CA a service of set for 24 h

^cAssays carried out for 24 h.

TABLE 2. Transesterification results using catalyst <i>n</i> -butyl stannonic acid									
			_			-h			

Entry	Compound	5 / DMT molar ratio ^a	Catalyst load ^b	Yield monoester (%)	Yield diester (%)
1	7	1.0	0.10	11 (49)	12 (11)
2	7	1.5	0.10	11 (43)	12 (41)
3	7	2.2	0.10	11 (14)	12 (72)
4	7	2.2	0.20	11 (6)	12 (85)
5	7	2.2	0.50	11 (-)	12 (92)
6	6	2.2	0.50	9 (-)	10 (99)

^aAmine:Tartrate molar ratio.

^bTi:Substrate molar ratio.

product 15. The resultant product 15 displays, as did the protected compound 5, the ability to react only with the protected tartrate through the hydroxyl group. Thus, 15 was reacted with the benzilidene acetal protected dimethyl tartrate 7 to give the transester 16. Protected dimethyltartrate 7 was chosen as the starting material for this study because, unlike the butanedione derivative 6, which requires strong acid treatment for its cleavage, the benzilidene acetal protecting group can be easily removed using mild hydrogenation conditions. In this way, the integrity of the rest of the molecule was ensured by the cleavage of **16** with Pd/C to give **17**. All the steps of this sequence have led to similar results to that achieved for the analog product 11, although butyl stannonic acid was used as catalyst for the transesterification reaction because of its readily availability and its capability to mainly produce symmetric bis-substituted tartrates through transesterification. The crude reaction product was then submitted to hydrogenation in presence of Pd/C as catalyst for the cleavage of the benzylidene acetal, giving product 17 as a white solid.

Catalytic Tests

The enantioselective epoxidation of different allylic alcohols with TBHP was performed at -20° C in presence of either **3**, **4**, **13**, **14** or **17** as chiral ligands and using Ti(OiPr)₄ as titanium source. Ligands **13** and **14**, containing the BOC protecting groups, were studied for comparison purposes, to contrast the enantio- and catalytic activity of ligands **3** and **4**, with free amino functionalities. These tests also allowed checking the different modifications carried out during consecutive protection, transesterification and deprotection reactions did not cause ligand razemization. The results have been summarized in table 3.

The best activity and enantioselectivity were found for the BOC protected ligands **13** and **14** (Table 3, entries 3 and 4). Using ligand **14** as the chiral catalyst with titanium tetraisopropoxide gave the epoxy alcohol in up to 70% ee. In contrast, using tartrates with a free amino group i.e. **3** and **4** (entries 1 and 2) led to the generation of lower epoxide yields and enantioselectivities, which could be caused by the formation of different titanium-tartrate derivative complexes when secondary amino groups, free from protective groups and accordingly with labile hydrogen, are present within the chiral ligand. In general, these results were repeated for the different substrates tested, independent of the structure of the oxidized allylic alcohol. These results suggest only moderate efficiency in the formation of the tartrate-titanium complex, the essential active catalytic species for the sharpless epoxidation catalyst.

On the other hand, it is particularly noteworthy that the tartrate-derived chiral ligand supported on silsesquioxane 17 shows a similar activity to that of the Boc-protected tartrate analog, although the most interesting result for this reaction lies in the reversed enantioselectivity showed by this ligand. The measured enantiomeric excess is in the same range than using ligand 13, but the achieved chiral induction is completely reversed, yielding an excess of the opposite enantiomer to the major one achieved with the rest of the L-(+)-dimethyl tartrate derivatives. Enantioreversion has been previously observed with several ligands for different reasons.^{22–28} For instance, the molar ratio between components²² or changing the reaction solvent²⁵ can cause the reversal of the enantioselectivity of certain catalysts. Immobilising on polymer supports has also been described to produce reverse enantioselectivity.26,27 Actually, Janda and coworkers²⁷ found enantioreversal induction in the epoxidation of 2-hexen-1-ol when using poly(ethylene glycol) transesterified chiral tartrates. These authors have shown that the Sharpless' catalyst enantioselection can be reversed depending on the size of the ester substituents at the tartrate ligands, so that if the substituent is bigger than 750 a.m.u. the sign of the optical rotation of the product is reversed. Bearing in mind the silsesquioxane fragment attached to the tartrate ligand is larger than 1,100 a.m.u., a similar enantioreversal behavior could also arise with this ligand. With regard to the reusability of the silsesquioxane-pendant tartrate chiral ligand, the



Scheme 5. Different routes for the cleavage of modified chiral tartrate protecting groups. i) H_2 , Pd/C 10%, MeOH. ii) TFA/ H_2 O, 5 min, r.t. iii) TFA, 40°C, 24 h.



Scheme 6. Immobilization of tartrate-derived ligands on halo-phenyl functionalized silsesquioxane materials. R = Ciclopentane. i) 2 (1.5 eq), Pyridine (0.2 eq), reflux in dichloromethane for 24 h. ii) 7 (1 eq), BuSnOOH (0.05 eq), reflux in Benzene for 24 h. iii) H₂, Pd/C in AcEt, r.t. overnight.

same was recovered from the reaction media, after epoxidation of cinnamyl alcohol, by precipitation with THF, washing with dichloromethane and drying before being used in a second assay (Table 3, entry 6). Results indicate the enantioselectivity of the complex is preserved well during the recycling test, leading to the same enantiomeric excess in the final glycidol product. On the other hand, the catalytic activity is greatly decreased for the reutilization test, since less than half the initial epoxide yield is achieved. This loss of catalytic activity could be related to the inactivation of a fraction of the chiral complex during the recycling test. Preliminary results on the epoxidation of different allylic alcohols indicate a similar behavior for other substrates, finding the same enantioselective reversion observed for cinnamyl alcohol.

Finally, in order to determine whether this is the cause of enantioreversion or just the presence of the benzyl group in the aminoalcohol used for transesterifying the chiral tartrate ligand, a new compound was prepared. In this case, *N*-benzyl *N*-methyl amino ethanol was used for the transesterification of dimethyl tartrate starting from **7** and carrying out the transesterification reaction in presence of butylstannonic acid (Scheme 7). The resultant product, obtained after acetal cleavage, **18** was used as chiral ligand in the asymmetric epoxidation of cinnamyl alcohol inducing the usual chiral configuration on to the

Entry ^a	Substrate	Ligand	Epoxide yield (%) ^b	Enantiomeric excess (%) ^c
1		3	49	17
2	P OH	4	64	28
3		13	56	50
4		14	72	70
5		17	51	-40^{d}
6		17	27	$-41^{\rm e}$
7		18	66	65
8	СССОН	13	57	47
9		14	61	57
10		13	25	44
11	On	14	37	57
12	\frown	13	29	45
13	ОН	14	48	60
14	ОН	13	9	48
15	$\wedge \not \land \wedge \land$	14	17	52

TABLE 3. Asymmetric epoxidation of different allylic alcohols using tartrate-derived ligands

^aReactions were performed for 1 h -20°C, using TBHP as oxidant.

^cEnantiomeric excess achieved over the (S,S) or (S) enantiomer determined by chiral HPLC or GC.

^dReversal enantioselectivity is achieved for the silsesquioxane supported chiral ligand.

^eRecycling test.

^bIsolated Yield.



Scheme 7. Tartrate derivative incorporating aromatic rings analogue to 17 without silsesquioxane pendant groups.

resultant phenyl glycidol (Table 3, entry 7). In this way, the enantioselectivity reversal observed for the POSS-functionalized material should be ascribed to the size of the silsesquioxane fragment more than to the presence of the aromatic ring.

In summary, straightforward strategy for modifying tartrates has been developed in order to attach the resultant chiral ligands onto properly-functionalized polyhedral oligomeric silsesquioxanes. The reaction conditions for transesterification were optimized to achieve either the monosubstituted or bis-substituted tartrate derivative as the sole product. The chiral tartrate-derived ligands so obtained were used in the asymmetric epoxidation of cinnamyl alcohol achieving up to 70% ee in the resulting epoxy-alcohol. C2-Symmetrical diesters 4 and 14 gave higher enantiomeric excesses than the asymmetric monosubstituted tartrate derivatives 3 and 13. Finally, the amino groups anchoring the tartrate-derived ligands to a silsesquioxane fragment result in a enantioselectivity reversal of the chiral ligand. Further studies on the application of this heterogeneization strategy to the anchoring of tartrate-derived ligands on the surface of silica supports are being performed.

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