The preparation of chiral titanium reagents: a comparison of new and known ligands

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(Received January 5, 1994)

Abstract

Allyltitanium compounds and Ti enolates derived from monocyclopentadienylchlorotitanium complexes with two chiral alkoxy ligands add with high enantioface discrimination to aldehydes. While two diacetone-D-glucose ligands are perfectly suited for aldol reactions, tartrate derived 1,4-diol ligands, available in both enantiomeric forms, give high induction for the allyltitanation only. The chelating 1,4-diol ligands with a fixed C(2)–C(3) bond are rather insensitive to structural changes, as opposed to diacetone glucose, where only minor structural modifications at the acetal carbons are tolerated. Crucial for high enantioselectivity is apparently an interligand interaction, which can either be effected by a 'small' Cp ligand and 'large' phenyl substituents or by a 'large' pentamethyl Cp and 'small' methyls. Experiments with new dibenzobicyclo[2.2.2]octane based 1,4-diol ligands show that the effect of intraligand strain on enantioselectivity is small in comparison with the impact of the interligand, Cp substituent, interaction. New X-ray evidence from the crystal structure analysis of a μ-oxo-bridged dimer shows that dioxolane-fixed seven-membered 1,3-dioxa-2-titanacycles are conformationally quite flexible. Explanations for the mechanism of asymmetric induction by these complexes, which are based on previous X-ray data, have therefore to be rated as less stringent than assumed before.

Key words: Chiral reagents; Titanium complexes; Allyl complexes; Enolate complexes

Introduction

The role of early transition metals in organic chemistry can be divided into redox processes, typical for transition metals, and Lewis acid functions, related to their often well defined coordination geometry. Titanium, a very popular representative because of its high natural abundance and low toxicity, is used for reductive C–C couplings [1], as catalyst for olefin polymerizations [2], or for oxidations with hydroperoxides, e.g. the famous Sharpless epoxidation [3]. Other applications include carbonyl olefinations [4], 1,2-addition of nucleophilic ligands, especially alkyl groups, to carbonyls [5], and Lewis acid catalysis for enantioselective ene-reactions [6], cycloadditions [7], as well as enantioselective allylstannylations of aldehydes [8]. The use of chiral Ti reagents for stereoselective addition of nucleophiles to carbonyl compounds is a subject which has been recently reviewed [9].

The Lewis acidity of Ti(IV) reagents can be attenuated efficiently with η_5-bound cyclopentadienyl ligands, as Ti compounds with four η_1-bound ligands are 8-electron complexes, monocyclopentadienyltitanium derivatives formally 12-electron, and titanocenes 16-electron complexes. We have discovered that the enantio- and diastereoselective addition of allyl groups and ester enolates to aldehydes is very efficiently effected by Ti reagents derived from monocyclopentadienyl-dialkoxy-titanium(IV) chlorides [10]. So far the best systems are complex **1** with two bis-acetonides of α-D-glucofuranose as chiral ligands [11] and the seven-membered titana-

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SSDI 0020-1693(94)03899-Y

cycle (*S*)-**2**/(*R*)-**2***, obtained from tartrate derived 1,4-diol ligands (Fig. 1).

Allyltitanium reagents **3** are obtained from **1** [11a], (*S*)-**2** or (*R*)-**2** [12] by transmetalation with unsubstituted (R′ = H) and terminally monosubstituted allyl–Grignard or allyl–Li compounds. Very fast allylic rearrangements and bond rotations ensure that the energetically favored allyltitanium isomer **3** with *trans*-double bond and titanium η_1-bound to the unsubstituted allyl terminus prevails. The organometallic precursor can therefore be either a mixture of all possible isomers, typical for allyl–Grignards, or a pure isomer, as obtained by lithiation of *cis*-2-butene [12]. Reaction with an aldehyde (RCHO) at −78 °C gives homoallylic alcohols **4** with good yields. While good enantioselectivity is achieved with **1** (e.g. 90% e.e. for R = Ph, R′ = H), the reagent of choice is (*S*)-**2**, not only for its even better enantiocontrol (95% e.e. for R = Ph, R′ = H), but also because the enantiomers can be obtained by using (*R*)-**2**. The almost exclusive formation of *anti*-isomers is best rationalized by a six-membered cyclic transition state with chair conformation (Fig. 2). Especially for chiral aldehydes, the allyltitanium compounds **3** derived from chlorides (*R*)-**2** and (*S*)-**2** are presently the most stereoselective and least substrate dependent reagents for aldehyde allylation, a subject which has recently been reviewed for metals other than titanium [13].

Titanium enolates derived from **1** or **2** are less reactive than the allyl derivatives **3**, and in addition to the ester enolates **5** obtained by transmetalation of Li enolates [14–16], imide enolates [15] and possibly also amide enolates, react with aldehydes affording β-hydroxy esters **6** of excellent enantiomeric and diastereomeric purity (Fig. 2). In this case, however, good results are only obtained with the diacetoneglucose derived complex **1**, e.g. 96% e.e. for R = i-butyl, R′ = H, R″ = t-butyl, compared to 78% e.e. for **5** derived from (*S*)-**2**. This difference, displayed by these closely related nucleophiles, adding with allylic 1,3-transposition to aldehydes, is most probably related to different transition state geometries. The high *syn*-preference of substituted (*E*)-enolates **5** implies a boat conformation, as opposed to the chair conformation deduced for the transition state of the allylation (see above). The enolate geometry of the Li enolates appears to be retained upon transmetalation at −78 °C, and (*Z*)-enolates therefore lead to the *anti*-diastereomers of **6** [15]. A change from *syn*- to *anti*-selectivity upon warming the enolate **5** derived from 2,6-dimethylphenyl propionate to −30 °C can thus be explained by an isomerization from the (*E*)- to the (*Z*)-enolate [15]. The reagents are again among the most stereoselective chiral enolates with 'external' chiral

*The reagents (*S*)-**2** (cat. No. 40182) and (*R*)-**2** (cat. No. 40180) were supplied by Fluka AG, CH-9470 Buchs, Switzerland.

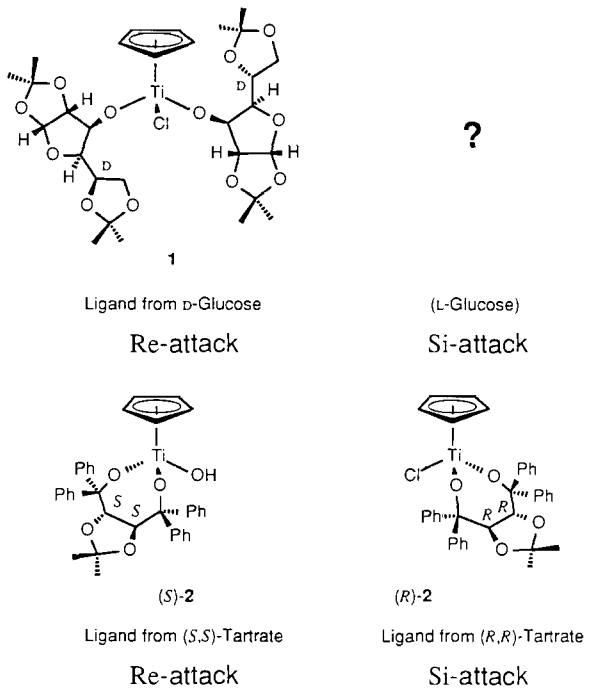


Fig. 1. Structures of chiral cyclopentadienyl-dialkoxy-chlorotitanium complexes.

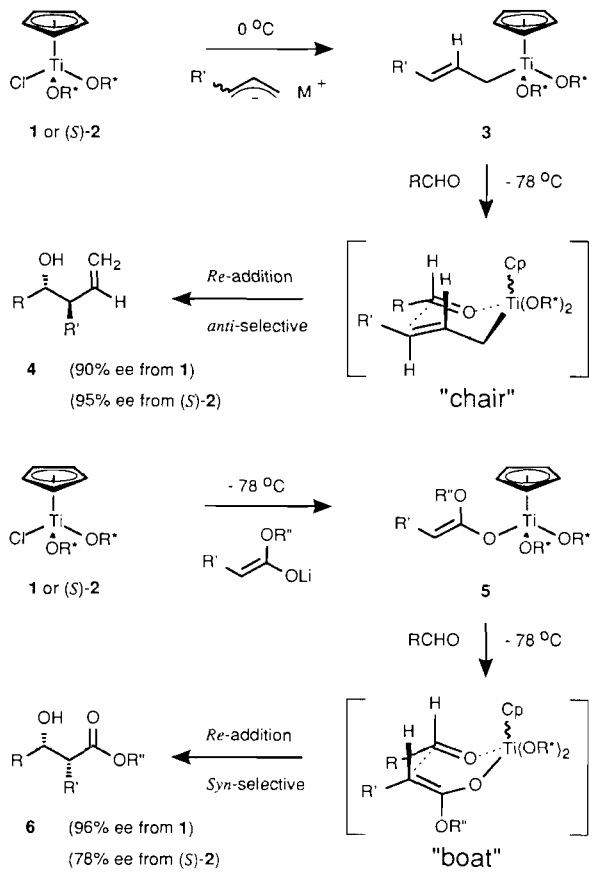


Fig. 2. Schemes of allyltitanation of aldehydes and aldol reactions with complexes **1** and **2**.

auxiliaries. Their performance is equaled only by rather sophisticated chiral boron enolates [17] and by some tin enolates [18]. In contrary to the allylation, a major drawback of these aldol reactions is that only the reagents **5** for Re addition are readily available, as no substitute for the costly L-glucose has yet been found (see Fig. 1). In the following our efforts to fill this gap by looking for new ligands, by modifying the successful structures, and by trying to understand the mechanism for the stereocontrol by **1** and **2** are described. Part of this work has either been published before in preliminary form [9, 10], or has been presented at conferences [19].

Experimental

General remarks

Melting points were determined in open capillaries, and are not corrected. Specific rotations ($[\alpha]_D$) were measured in a 1 ml microcuvette (10 cm) on a Perkin-Elmer polarimeter 241 at ambient temperature (20–25 °C). Capillary GLC analyses were done on a Carlo-Erba Strumentazione HRGC 5300 chromatograph using Chirasil-Val-III columns [20] (50 m, 0.32 mm diameter, Altech Applied Science Labs, Deerfield, IL; Serial No. 986 L). Considerable variations in retention times (t_R) and separation have been observed for different columns. Before injection, secondary alcohols and β-hydroxy acids were derivatized with *N*-isopropyl-isocyanate [20], α-amino-β-hydroxy esters with trifluoroacetanhydride [20a, c]. The accuracy and reproducibility of such determinations is ±0.1 to 0.3%. ^{1}H NMR and ^{13}C NMR spectra were recorded on either a Bruker AC-250 (250 and 62.9 MHz, respectively) or on a Bruker AM-400 (400 and 100.6 MHz, respectively) spectrometer.

Cyclopentadienyltitanium trichloride (**8**) was prepared from Cp_2TiCl_2 and $TiCl_4$ [21] and (pentamethylcyclopentadienyl)titanium trichloride resulted from reaction of pentamethyl-trimethylsilyl-cyclopentadiene and $TiCl_4$ [22]; both compounds were freshly sublimed before use. Allylmagnesium chloride in THF was purchased from Alfa Products; its content was checked by titration [23]. Crotylmagnesium chloride was prepared according to O'Brien *et al.* [24], filtered from precipitated salts, and titrated [23]. THF, diethyl ether, toluene and saturated hydrocarbons were distilled from Na-benzophenone ketyl for drying.

General procedure for the derivatization of alcohols and β-hydroxy acids with N-isopropyl-isocyanate (GLC analysis)

A solution of substrate (10–20 mg) in CH_2Cl_2 (2 ml) and *N*-isopropyl-isocyanatc (1 ml) is placed in a screwcap ampoule with a high pressure safety valve. After heating for 20 min to 1 h in an oil bath of 100 °C with magnetic stirring, the volatile components of the cooled mixture are evaporated in a stream of dry Ar. The residue is redissolved in CH_2Cl_2 (5 ml), and 0.2 μl of this solution are injected for GLC analysis [20].

Preparation of ligands

Bis[(1S)-(1-ethoxycarbonyl)ethyl] fumarate (59) [25]

A solution of fumaric acid dichloride (160.65 g, 1.05 mol), ethyl (*S*)-lactate (**58**, 497 g, 4.2 mol) and hydroquinone (175 mg, 1.6 mmol) in 2.5 l of CH_2Cl_2 was heated under reflux while a stream of Ar was passed through the solution. After 44 h the mixture was cooled to −20 °C and Et_3N (213.5 g, 2.17 mol) was added within 2 h. The mixture was then left for 5 days in a freezer at −10 °C before being washed with H_2O (2×500 ml), 1 N HCl (3×200 ml), 2 N NaOH (2×200 ml) and saturated NaCl solution (2×300 ml). Drying (Na_2SO_4) and evaporation of solvent was followed by distillation (7 mbar). After collecting 44.8 g of impure material containing ethyl [(1*S*)-(1-ethoxycarbonyl)ethyl] fumarate (**60**), 186.97 (56%) of pure **59** were distilled at 140 °C, followed by 20.99 g of less pure material.

Physical data of 59. ^{1}H NMR (250 MHz, $CDCl_3$): 1.30 (t, J=7, 2 OCH_2CH_3); 1.58 (d, J=7, 2 CH_3CHO); 4.23 (q, J=7, 2 OCH_2CH_3); 5.20 (q, J=7, 2 CH_3CHO); 6.99 (s, H–C(2), H–C(3)). ^{13}C NMR (62.9 MHz, $CDCl_3$): 170.1 (2 CO_2Et); 164.0 (C(1), C(4)); 133.6 (C(2), C(3)); 69.5 (2 CH_3CHO); 61.6 (2 OCH_2CH_3); 16.9 and 14.1 (2 CH_3 each).

Physical data of 60. ^{1}H NMR (250 MHz, $CDCl_3$): 1.28 and 1.32 (2t, J=7, 2 OCH_2CH_3); 1.55 (d, J=7, CH_3CHO); 4.22 and 4.27 (2q, J=7, 2 OCH_2CH_3); 5.18 (q, J=7, CH_3CHO); 6.93 (s, H–C(2), H–C(3)). ^{13}C NMR (62.9 MHz, $CDCl_3$): 170.2 (CO_2Et); 164.8 and 164.3 (C(1), C(4)); 134.7 and 132.6 (C(2), C(3)); 69.5 (CH_3CH); 61.6 and 61.4 (2 $OCHCH_3$); 16.9 and 14.1 (2 CH_3CH_2O, CH_3CHO).

Bis[(1S)-(1-ethoxycarbonyl)ethyl](7R,trans)-dibenzo-b,e-bicyclo[2.2.2]octane-7,8-dimethanoate (57) [26]

Fumarate **59** (80.73 g, 255.2 mmol) and anthracene (54.7 g, 306.9 mmol) were dissolved in 1.3 l of boiling toluene, and the mixture was heated under reflux for 12 days. After evaporation of solvent, the residue was redissolved in EtOAc (600 ml). Upon cooling in an ice-bath anthracene (4.4 g) crystallized and was collected by filtration. The filtrate was evaporated to a volume of approximately 300 ml. Addition of hexane (300 ml) and cooling to 0 °C gave 81.8 g (63%) of adduct **57**, containing 4.9 mol% (1.8% by weight) of anthracene. A second crop (24.0 g, 19%) of pure **57** could be obtained by crystallization of the mother liquor from AcOEt/hexane.

Physical data of 57. M.p. 100–100.5 °C. ^{1}H NMR (250 MHz, $CDCl_3$): 1.23 (t, J=7; 2 CH_3CH_2O); 1.43 (d, J=7, 2 CH_3CHO); 3.40 (b, $w_{1/2}\approx 4$, H–C(7), H–C(8));

4.20 (q, $J=7$, 2 CH_3CH_2O); 4.81 (b, $w_{1/2}\approx4$, H–C(1), H–C(4)); 5.0 (q, $J=7$, 2 CH_3CHO); 7.0–7.25 and 7.25–7.5 (2m, 4H each, H-arom). ^{13}C NMR (62.9 MHz, $CDCl_3$): 172.1 and 170.9 (4 CO_2R); 142.8 and 140.2 (C(2), C(3), C(5), C(6)); 126.8, 126.6, 126.0 and 123.8 (8 CH-arom.); 69.4 (2 CH_3CHO); 61.7 (2 CH_3CH_2O); 48.1 and 47.2 (C(1), C(4), C(7), C(8)); 17.5 and 14.6 (2 CH_3 each).

*Dimethyl (7R,trans)-dibenzo-b,e-bicyclo[2.2.2]octane-7,8-dimethanoate ((R)-**61**)*

Methanesulfonic acid (73 ml) was added at r.t. to a mixture of **57** (108.3 g, 2% anthracene, 214.6 mmol) in CH_3OH (2.2 l). The mixture was stirred at 50 °C for 5 days. After evaporation of solvent at reduced pressure to ≈1/3 of the volume, AcOEt was added, and the solution was washed with H_2O (400 ml), 10% aq. $NaHCO_3$ (300 ml) and sat. NaCl solution (3×400 ml). ^1H NMR analysis of the residue of the dried (Na_2SO_4) organic phases (77.2 g) showed, that the content of anthracene was essentially unchanged (≈2.8%). Upon addition of CH_3OH (500 ml) and warming to 45 °C most of the crude product was dissolved. After cooling to r.t. and addition of H_2O (70 ml) 1.3 g of insoluble material (mostly anthracene) was removed by filtration. Addition of a further 50 ml of H_2O led to the crystallization of **57** forming a thick suspension, which was filtered after the addition of 500 ml of CH_3OH/H_2O (1:1) and cooling to 0 °C. Drying gave 66.2 g (94%) of (*R*)-**57** containing ≈1% of anthracene (^1H NMR); m.p. 83–85 °C; $[\alpha]_D=+26.7$ ($c=2.4$, EtOH). An analytical sample was obtained by chromatography on silica gel (hexane/EtOAc = 4:1); m.p. 89–90 °C, $[\alpha]_D=+28.0$ ($c=2.4$, EtOH); lit. [27]: m.p. 90 °C; $[\alpha]_D=+26$ ($c=2$, EtOH). IR (KBr): 3070w, 3040w, 3020w, 2980w, 2955w, 2930w, 2850w, 1733s, 1585w, 1485w, 1468m, 1460m, 1437m, 1297s, 1263s, 1220s, 1208s, 1114m, 1090w, 1017s, 958w, 945w, 930w, 903w, 868w, 837w, 798w, 784m, 763m, 752s, 676w, 640w, 620w, 590w, 547m, 435w. ^1H NMR (400 MHz, $CDCl_3$): 3.43 (m, $w_{1/2}\approx5$, H–C(7), H–C(8)); 3.63 (s, 2 OCH_3); 4.75 (m, $w_{1/2}\approx5$, H–C(1), H–C(4)); 7.05–7.15 (m, 4H); 7.2–7.3 (m, 2H) and 7.3–7.38 (m, 2H) (H-arom.). ^{13}C NMR (62.9 MHz, $CDCl_3$): 171.6 (2 CO_2Me); 140.9 and 139.2 (C(2), C(3), C(5), C(6)); 125.3, 125.2, 123.4 and 122.6 (CH-arom.); 51.1 (2 OCH_3); 46.6 and 45.5 (C(1), C(4), C(7), C(8)).

Dimethyl (7R,trans)-dibenzo-b,e-bicyclo[2.2.2]octane-7,8-dimethanoate ((±)-**61**) [27]*

To a solution of (7*R**,*trans*)-dibenzo-*b*,*e*-bicyclo-[2.2.2]octane-7,8-dicarboxylic acid ((±)-**64**) [28] (5 g, 16.9 mmol) in CH_3OH (10 ml) and 1,2-dichloroethane (20 ml), CH_3SO_3H (1 ml) was added. The mixture was boiled under reflux for 2 days, diluted with H_2O (70 ml) and extracted with CH_2Cl_2 (40 ml). The organic phases were washed with H_2O (2×50 ml), dried (Na_2SO_4) and evaporated. Chromatography (400 g of silica gel, hexane/EtOAc = 5:1) of the residue afforded 5.3 g (96%) of (±)-**61**. An analytical sample was crystallized from CH_3OH/H_2O; m.p. 105.5–106.5 °C; lit [27] 107 °C. IR (KBr): 3080w, 3045w, 3025w, 2990w, 2960w, 2840w, 1733s, 1685w, 1483w, 1470m, 1460m, 1432m, 1382w, 1336w, 1310s, 1282m, 1268s, 1220s, 1195s, 1168m, 1112m, 1019s, 1000w, 955w, 920w, 912w, 900w, 870w, 836w, 802w, 784m, 763s, 733w, 663w, 640w, 628w, 600w, 590w, 552w, 530w, 435w. ^1H NMR (400 MHz, $CDCl_3$, addition of ≈2 equiv. of (+)-2,2,2-trifluoro-1-(9′-anthryl)ethanol [29]): among other signals 3.29 (m, $w_{1/2}\approx4$, H–C(7), H–C(8), (*R*)-**61**); 3.325 (m, $w_{1/2}\approx4$, H–C(7), H–C(8), (*S*)-**61**); 3.425 and 3.44 (2s, OCH_3).

*(7R,trans)-α,α,α′,α′-Tetramethyl-dibenzo-b,e-bicyclo[2.2.2]octane-7,8-dimethanol ((R)-**62**)*

To a solution of (*R*)-**61** (10.0 g, 31 mmol) in 200 ml of dry Et_2O, cooled to 5 °C, a 2.35 M solution of CH_3MgBr in Et_2O (76 ml, 178.6 mmol) was added at a rate that the temperature did not exceed 10 °C (25 min). By stirring at r.t. for 1 h the initially formed precipitate was transformed into a finely dispersed suspension. The mixture was boiled for 2 h under reflux, cooled to 20 °C, and hydrolyzed by careful addition of sat. NH_4Cl solution (180 ml). After the addition of 2 N HCl (330 ml) the suspension was filtered using Celite®. The aqueous phase was separated and the organic layer was washed with sat. NaCl solution (3×400 ml), dried (Na_2SO_4), and evaporated. The residue (9.54 g) was crystallized from EtOAc/hexane affording 4.37 g (40%) of (*R*)-**62**, retaining ≈7.5% of solvents (EtOAc/Et_2O) after drying for 3 days at high vacuum. Chromatography (200 g of silica gel, hexane/EtOAc = 2:1) of the mother liquor (5.03 g) and crystallization of the pure fractions (3.0 g) gave an additional 1.75 g (16%) of (*R*)-**62**; m.p. 144.5–145.5 °C, $[\alpha]_D=+57.2$ ($c=3.2$, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): 0.4 and 1.5 (2s, 4 CH_3); 2.13 (m, $w_{1/2}\approx4$, H–C(7), H–C(8)); 3.83 (s, 2 OH); 4.31 (m, $w_{1/2}\approx5$, H–C(1), H–C(4)); 7.0–7.13 (m, 5 main peaks, 4H), 7.17–7.22 (m, 2 main peaks, 2H), 7.25–7.3 (m, 2 main peaks, 2H) (H-arom.). ^{13}C NMR (62.9 MHz, $CDCl_3$): 144.2 and 141.8 (C(2), C(3), C(5), C(6)); 126.0, 125.6, 124.8 and 123.5 (CH-arom.); 72.6 (C(α), C(α′)); 51.5 and 47.4 (C(1), C(4), C(7), C(8)); 30.7 and 25.2 (4 CH_3).

Racemic (±)-**62** was prepared analogously from racemic diester (±)-**61**: m.p. 230–231 °C. ^1H NMR (400 MHz, $CDCl_3$, addition of ≈2 equiv. of (+)-2,2,2-trifluoro-1-(9′-anthryl)ethanol [29]): among other signals 0.07/0.095 and 1.15/1.17 (4 CH_3); 1.69/1.785 (H–C(7), H–C(8)); 4.035/4.06 (H–C(1), H–C(4)).

*(7R,trans)-α,α,α',α'-Tetraphenyl-dibenzo-b,e,-bicyclo[2.2.2]octane-7,8-dimethanol ((R)-**63**)*

To a solution of (*R*)-**61** (10.0 g, 31 mmol) in 67 ml of dry Et_2O, cooled to 2 °C, 118 ml (177 mmol) of a 1.5 M ethereal solution of PhMgBr were added at such a rate that the temperature did not exceed 10 °C (20 min). The initially formed precipitate was dissolved upon stirring for 2 h at r.t. After boiling for 2 h under reflux, the mixture was cooled to 10 °C and hydrolyzed by careful addition of sat. NH_4Cl solution (200 ml). The suspension was dissolved by the addition of 2 N HCl (330 ml). The aqueous phase was separated, and the organic layer was washed with sat. NaCl solution, dried (Na_2SO_4) and evaporated. Chromatography (1 kg of silica gel, hexane/EtOAc = 19:1) of the residue (25.3 g) afforded 10.7 g (60%) of (*R*)-**63**. A sample (3.7 g) was crystallized from CH_3OH/H_2O, yielding 3.3 g (*R*)-**63**; m.p. 123–126 °C (decomp.); $[\alpha]_D = +32$ ($c = 1.6$, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): 1.33 (s, 2 OH); 3.93 (m, $w_{1/2} \approx 5$, H–C(7), H–C(8)); 4.34 (m, $w_{1/2} \approx 5$, H–C(1), H–C(4)); 6.4–6.53 (m, 2 main peaks, 2H); 6.72–6.9 (m, 6H); 6.9–7.05 (m, 3 main peaks, 2H); 7.05–7.45 (m, 18H) (H-arom.). ^{13}C NMR (62.9 MHz, $CDCl_3$): 147.7, 146.1, 144.5 and 141.5 (C(2), C(3), C(5), C(6), 4 C-arom.); 127.9, 127.7, 126.5, 126.3, 126.1, 125.5, 124.9 and 123.8 (CH-arom.); 80.4 (C(α), C(α')); 48.6 and 48.1 (C(1), C(4), C(7), C(8)).

Racemic (±)-**63** was prepared analogously from racemic diester (±)-**61**: m.p. 145–150 °C (decomp). ^1H NMR (400 MHz, $CDCl_3$, addition of ≈2 equiv. of (+)-2,2,2-trifluoro-1-(9'-anthryl)ethanol [29]): among other signals 1.44/1.485 (OH), 3.86/3.875 (not baseline separated, H–C(7), H–C(8)); 4.275/4.33 (H–C(1), H–C(4)).

Synthesis of complexes and X-ray analysis

*Cyclopentadienyl[(7R,trans)-α,α,α',α'-tetramethyl-dibenzo-b,e-bicyclo[2.2.2]octane-7,8-dimethanolato-O(α),O(α')]chlorotitanium ((R)-**54**)*

A solution of $CpTiCl_3$ (**8**, 1.206 g, 91%, 5 mmol) and (*R*)-**62** (1.741 g, 92.5%, 4.99 mmol) in dry toluene (160 ml) was heated for 41 h to 100 °C, while a slow stream of Ar was passed over the surface and through a condenser. The solvent was evaporated under reduced pressure. According to ^1H NMR (250 MHz, $CDCl_3$) the crude material (*R*)-**54** contained 6% of ligand (*R*)-**62** and approximately 15% of another CpTi(IV) complex (s, 6.61 ppm). ^1H NMR (250 MHz, $CDCl_3$): 0.37, 0.40, 1.42 and 1.50 (4 CH_3); 2.03–2.12 and 2.56–2.67 (2m, H–C(7), H–C(8)); 4.29 (m, $w_{1/2} \approx 7$, H–C(1), H–C(4)); 6.37 (s, C_5H_5); 6.93–7.35 (m, H-arom.). ^{13}C NMR (62.9 MHz, $CDCl_3$): 143.4, 143.3, 142.6 and 142.1 (C(2), C(3), C(5), C(6)); 126.0, 125.9, 125.6, 125.5, 125.3, 125.1, 125.0, 124.8, 123.8 and 123.6 (CH-arom.); 114.9 (C_5H_5); 94.3 and 94.2 (C(α), C(α')); 54.2, 52.6, 47.9 and 47.7 (C(1), C(4), C(7), C(8)); 29.9, 29.6, 24.5 and 23.5 (4 CH_3).

*Cyclopentadienyl[(7R,trans)-α,α,α',α'-tetraphenyl-dibenzo-b,e-bicyclo[2.2.2]octane-7,8-dimethanolato-O(α),O(α')]chlorotitanium ((R)-**55**)*

From a mixture of diol (*R*)-**63** (2.57 g, 4.5 mmol) and 2.6 g of powdered molecular sieves 4 Å in dry toluene (200 ml), 50 ml of solvent were distilled at normal pressure (Ar). The cooled mixture was filtered under Ar, and Et_3N (1.49 ml, 10.7 mmol) and $CpTiCl_3$ (**8**, 1.17 g, 91%, 4.85 mmol) were added. After stirring for 90 h at 45 °C (Ar), the mixture was cooled, and precipitated Et_3N hydrochloride was filtered off under Ar. The solvent was evaporated at reduced pressure, and the brownish-orange residue was dried at high vacuum. According to ^1H NMR (250 MHz, $CDCl_3$) the crude (*R*)-**55** contained ≈9.5% of free ligand (*R*)-**63** and an additional CpTi(IV) complex (s, 6.63 ppm). ^1H NMR (250 MHz, $CDCl_3$): 3.84 and 3.92 (2d, $J = 8$, H–C(7), H–C(8)); 4.10 and 4.28 (2m, $w_{1/2} \approx 3$, H–C(1), H–C(4)); 5.96 (s, C_5H_5); 6.07 and 6.21 (2d, $J = 8$, 1H each); 6.37 (td, $J = 8$ and 1, 1H); 6.45–7.7 (m, 25H) (H-arom.). ^{13}C NMR (62.9 MHz, $CDCl_3$): 147.6, 144.8, 143.7, 143.6, 143.2, 141.7 and 140.2 (C(2), C(3), C(5), C(6), 4 C-arom.); 129.3, 129.0, 128.6, 128.3, 128.2, 127.9, 127.7, 127.4, 127.3, 127.2, 127.0, 126.7, 126.5, 126.4, 125.4, 125.3, 125.1, 124.9, 124.7, 124.6, 124.3 123.9, 122.2, 120.8 and 120.6 (CH-arom.); 116.1 (C_5H_5); 98.7, 98.4 (C(α), C(α')); 48.7, 48.6, 48.5 and 47.9 (C(1), C(4), C(7), C(8)).

*(Pentamethylcyclopentadienyl)[(4R,trans)-2,2,α,α,α',α'-hexamethyl-1,3-dioxolane-4,5-dimethanolato-O(α),O(α')]chlorotitanium ((R)-**50**) [12]*

To a solution of (pentamethylcyclopentadienyl)-titanium trichloride (0.87 g, 3 mmol) in dry toluene (70 ml) (4*R*,*trans*)-2,2,α,α,α',α'-hexamethyl-1,3-dioxolane-4,5-dimethanol [12, 30] (**32**, 0.65 g, 2.98 mmol) was added. The orange solution was stirred for 1 h at r.t., while a stream of Ar was passed through the liquid. Heating under reflux with a stream of Ar passing through the condenser was continued for 16 h. The resulting solution of (*R*)-**50** was concentrated at reduced pressure. Crystals suited for X-ray analysis (see Table 1) were formed upon further slow evaporation of toluene at r.t. in a stream of dry Ar (5 days).

*μ-Oxo-bis{cyclopentadienyl[(4R,trans)-2,2-dimethyl-α,α,α',α'-tetraphenyl-1,3-dioxolane-4,5-dimethanolato-O(α),O(α')]titanium} ((R)-**56**)*

To a well stirred suspension of partially dissolved (*R*)-**2** (25.1 g, 40.9 mmol) in Et_2O (500 ml), Et_3N (6.0 ml, 4.365 g, 43.1 mmol) was added, followed by the

dropwise addition of H_2O (370 mg, 20.56 mmol) within 1 min. The suspension was stirred for 2.5 h, the Et_2O was removed by evaporation and the residue was triturated with pentane (1 l, 2×400 ml). The pentane extracts were filtered through $MgSO_4$. Evaporation of the filtrate gave 21.0 g (87%) of (*R*)-**56** as a faintly yellow powder. *Anal.* Calc. for $C_{72}H_{66}O_9Ti_2$ (1171.11): C, 73.85; H, 5.68. Found: C, 73.23; H, 5.93%. ^1H NMR (250 MHz, $CDCl_3$): 0.43 and 0.54 (2s, $(CH_3)_2$); 4.82 and 5.0 (2d, $J=7$, H–C(4), H–C(5)); 5.75 (s, C_5H_5); 7.0–7.6 (m, H-arom.).

The μ-oxo-dimer (*R*)-**56** can also be obtained by shaking a solution of chloride (*R*)-**2** in CH_2Cl_2 with 2 equiv. of NaOH in H_2O (91% yield). Shaking of an NMR sample of (*R*)-**2** for a short time with 45% NH_4F solution gives (*R*)-**56** as the only product, according to NMR. The oxide (*R*)-**56** is an apolar compound, well soluble in most aprotic solvents suitable for crystallization. It is therefore difficult to obtain crystals from optically pure (*R*)-**56**. Crystals suited for X-ray analysis could, however, be obtained, when Et_2O vapor was diffused into a $CDCl_3$ solution (NMR sample) of racemic **56**, prepared by mixing equimolar amounts of (*R*)-**56** and (*S*)-**56**. No ligand exchange was observed, even at 60 °C (^1H NMR).

Crystal structure analyses of (R)-50 and (±)-56

Crystal data of (*R*)-**50** and (±)-**56** are given in Table 1. The crystal of (*R*)-**50** was cooled in a stream of N_2 to -84 ± 3 °C, to avoid decomposition during the measurement. Cell constants were determined by a least-squares fit to the Θ values of 25 independent reflections. Data were reduced and Lorentz, polarization and decomposition corrections were applied. The structures were solved by direct methods using the Enraf-Nonius Structure Determination Package [31]. In (*R*)-**50** all non-H atoms, in (±)-**56** only the heavier atoms Ti and Cl were refined anisotropically. Scattering factors were taken from the International Tables [32]. Figures were drawn using the program ORTEP [33].

Allyltitanation of aldehydes

(1S)-1-Phenyl-3-buten-1-ol ((S)-10)

A. Using complex (R)-54. To a solution of crude (*R*)-**54** (prepared from 0.925 mmol of diol (*R*)-**62**) in 20 ml of dry Et_2O, allylmagnesium chloride (1.23 ml of a 0.75 M solution in THF, 0.925 mmol) was added at 0 °C within 5 min (Ar). After stirring for 1 h at 0 °C, the mixture was filtered through dried Celite® under Ar pressure. Evaporation of a sample (5 ml) of the filtrate and ^1H NMR analysis (250 MHz, C_6D_6) showed the following peaks of the allyltitanium complex: 0.08, 0.16, 1.13 and 1.20 (4s, 4 CH_3); 1.8 and 2.63 (2m, H–C(7), H–C(8)); 3.1–3.7 (b, 2H–C(1′), 2H–C(3′)); 4.0 and 4.05 (2m, H–C(1), H–C(4)); 5.76 (s, C_5H_5); 6.10 (quint., $J=11$, H–C(2′)); 6.6–7.1 (m, H-arom.). The remaining solution was left at r.t. for 105 min, and 10 ml were cooled −78 °C (Ar) before the addition of benzaldehyde (98 mg, 0.925 mmol). After stirring for 3 h at −78 °C, 45% aq. NH_4F solution was added, and the mixture was stirred vigorously at r.t. overnight. After filtration, the aqueous phase was separated and extracted with Et_2O. The organic layer was washed with 10% NaCl solution (3×), dried (Na_2SO_4) and evaporated. Chromatography (22 g of silica gel, hexane/EtOAc = 4:1) of the residue (349 mg) afforded 79 mg (57%) of (*S*)-**10** and ligand (*R*)-**62** (247 mg). After derivatization with *N*-isopropyl-isocyanate according to the general procedure, analysis by capillary GLC (Chirasil-Val [20], carrier 70 kPa, 160 °C) showed a 5% excess of (*S*)-**10**: $t_R=14.57$ min (52.5%); (*R*)-**10**: $t_R=14.28$ min (47.5%).

B. Using complex (R)-55. To a solution of crude (*R*)-**55** (prepared from 4.332 mmol of diol (*R*)-**63**) in 150 ml of dry Et_2O, allylmagnesium chloride (5.2 ml of a 0.75 M solution in THF, 3.899 mmol) was added at 3–4 °C (Ar). After stirring for 2 h at 0 °C, the resulting suspension was filtered through dried Celite® under Ar pressure. The filtrate was cooled to −78 °C before benzaldehyde (321.8 mg, 3.032 mmol) was added. After stirring for 2 h at −78 °C, the reaction was quenched by the addition of 45% aq. NH_4F (35 ml). Workup, purification and analysis as above afforded diol (*R*)-**63** (1.9 g, 77%) and 359 mg (79%) of (*S*)-**10** with 87% excess of (*S*)-**10**, according to capillary GLC; $[\alpha]_D=-43.6$ ($c=6.7$, benzene).

(1S,2S)-1-Phenyl-2-methyl-3-buten-1-ol ((S)-47)

A. Using complex (R)-54. To a solution of crude complex (*R*)-**54** (prepared from 4.867 mmol of diol (*R*)-**62**) in 100 ml of dry Et_2O, crotylmagnesium chloride (7.62 ml of a 0.575 M solution in Et_2O, 4.38 mmol) was added at 2 °C within 5 min (Ar). After stirring for 1.5 h at 2 °C, the orange–brown suspension was cooled to −78 °C, and benzaldehyde (413 mg, 3.893 mmol) was added. The mixture was stirred for 2 h 45 min at −75 °C and then quenched by the addition of 45% aqueous NH_4F (40 ml). Workup as described above for (*S*)-**10** gave 2.6 g of crude mixture, which was triturated with pentane (35 ml). The precipitated diol ligand (*R*)-**62** was removed by filtration. Distillation of the residue of the filtrate (bulb-to-bulb, 0.4 mbar, 150 °C) afforded a 91:9 mixture of (*S*)-**47** (*anti*) and *syn*-epimer (537 mg, 85%). The epimer ratio was determined by ^1H NMR (250 MHz, $CDCl_3$): (*S*)-**47** (*anti*): 0.86 (d, $J=7$, CH_3); 2.20 (d, $J=3$, OH); 2.4–2.6 (m, H–C(2)); 4.34 (dd, $J=10$ and 3, H–C(1)); 5.1–5.3 (m, 3 main peaks, 2H–C(4)); 5.81 (ddd, $J=16$, 12 and 8, H–C(3)); 7.2–7.5 (m, C_6H_5); (*syn*): 1.03 (d, $J=7$, CH_3); 2.02 (d, $J=4$, OH); 2.5–2.7 (m, H–C(2)); 4.6 (dd, $J=6$

TABLE 1. Crystal data

	(*R*)-**50**	(±)-**56**
Formula	$C_{21}H_{35}ClO_4Ti$	$C_{72}H_{66}O_9Ti_2 \cdot 2(CDCl_3)$
Molecular weight	434.86	1411.88
Crystal system	monoclinic	triclinic
Space group	$P2_1$	$P\bar{1}$
a (Å)	8.857(1)	13.536(2)
b (Å)	20.684(3)	13.827(2)
c (Å)	12.936(2)	20.741(3)
α (°)		97.75(1)
β (°)	98.21(1)	108.48(1)
γ (°)		106.77(1)
V (Å^3)	2346(1)	3414(2)
Z	4	2
D_{calc} (g cm^{-3})	1.231	1.373
Crystal size (mm)	0.80×0.70×0.50	0.57×0.137×0.12
T (°C)	−84±3	23
Diffractometer	Philips PW1100	Philips PW1100
Radiation (graphite monochromated)	Mo Kα	Mo Kα
Wavelength (Å)	0.7107	0.7107
Scan mode	$\Theta/2\Theta$	$\Theta/2\Theta$
μ (cm^{-1})	9.50	5.24
F(000)	1044	1468
Scan range (2θ)	6–60	6–44
No. measured reflections	7350	8631
No. unique reflections	7138	8400
No. observed reflections ($I > 2\sigma(I)$)	5772	5162
R(int)	0.039	0.040
Refinement method	full matrix	full matrix
Weighting scheme	$1/\sigma^2(\|F_o\|)$	$1/\sigma^2(\|F_o\|)$
Hydrogen atoms	not located	not located
No. parameters	486	405
R	0.062	0.088
R_w	0.065	0.091
Max./min. density in final difference map (e Å^{-3})	0.722/−0.558	1.232/−0.983

and 4, H–C(1)); 4.95–5.1 (m, 2 main peaks, 2H–C(4)); 5.65–5.8 (m, H–C(3)); 7.2–7.5 (m, C_6H_5). After derivatization with *N*-isopropyl-isocyanate according to the general procedure, analysis by capillary GLC (Chirasil-Val [20], carrier 50 kPa, 130 °C) showed (1*R*,2*R*)-**47** (*anti*), t_R = 79.9 min (36.6%); (1*S*,2*S*)-**47** (*anti*) + (1*R*,2*S*)-*syn*, t_R = 82.8 and 83.5 min (58%, not baseline separated); (1*S*,2*R*)-*syn*, t_R = 86.4 min (5.4%). Using the diastereomer ratio (*anti*/*syn* = 91:9) determined by ^{1}H NMR, the enantiomeric excess of (*S*)-**47** (*anti*) is 19%, and ~21% for the *syn*-epimer.

B. Using complex (*R*)-*55*. To a solution of crude complex (*R*)-**55** (prepared from 4.114 mmol of diol (*R*)-**63**) in 80 ml of dry Et_2O, crotylmagnesium chloride (2.3 ml of a 1.63 M solution in Et_2O, 3.75 mmol) was added at 4 °C within 1 min (Ar). After stirring for 2 h at 0 °C, the red–brown suspension was cooled to −75 °C, and benzaldehyde (349 mg, 3.288 mmol) was added. The mixture was stirred for 2.5 h at −75 °C and then quenched by the addition of 45% aq. NH_4F (35 ml). Workup, purification and analysis as above afforded recovered ligand (*R*)-**63** and 450 mg (84%) of a 95:5 mixture of (*S*)-**47** (*anti*, 82% e.e.) and *syn*-epimer.

Aldol reactions

2,4-Dimethyl-3-pentyl acetate (36c)

To a solution of 2,4-dimethyl-3-pentanol (17.93 g, 21.6 ml, 154.3 mmol) in 160 ml of dry Et_2O, n-BuLi (100 ml of an approximately 1.55 M solution in hexane, 155 mmol) was added at 0–5 °C (Ar). Acetyl chloride (18.17 g, 231.5 mmol) dissolved in Et_2O (50 ml) was then slowly added at 0 °C. After warming to r.t., the reaction was quenched with sat. aq. NH_4Cl (100 ml). The aqueous phase was extracted with Et_2O (250 ml) and the organic phases were washed with 10% $NaHCO_3$ solution and sat. NaCl solution, and dried (Na_2SO_4). Distillation (~90 mbar, 82–84 °C, 20 cm Vigreux column) gave 14.78 g (52%) of ester **36c** (≈87% according to GLC) and a further 3.63 g (1.4%) of **36c** (≈97%). ^{1}H NMR (250 MHz, $CDCl_3$): 0.87 and 0.89 (2d, *J* = 7,

2 (CH_3)$_2$CH); 1.75–1.95 (m, 2 (CH_3)$_2$C*H*); 2.08 (s, CH_3CO); 4.59 (t, J=6, CHO).

*2,6-Di-tert-butyl-4-methoxyphenyl acetate (**36d**)*

To a solution of 2,6-di-tert-butyl-4-methoxyphenol (16.74 g, 70.8 mmol) in dry THF (70 ml), n-BuLi (46 ml of an approximately 1.55 M solution in hexane, 71 mmol) was added at 0 °C (Ar). After stirring at 0 °C for 30 min, acetyl chloride (8.3 g, 105.7 mmol) was added and the mixture was stirred at r.t. overnight. The reaction was quenched by the addition of sat. aq. NH_4Cl (100 ml), and the mixture was extracted with Et_2O (2×250 ml). The organic layer was washed with 10% $NaHCO_3$ solution and sat. NaCl, dried ($MgSO_4$) and evaporated. Chromatography (250 g of silica gel, hexane/EtOAc = 10:1) of the residue (22.5 g) gave 4.607 g (23%) of slightly impure **36d** and 3.792 g (19%) of pure **36d**, which was sublimed (10^{-2} mbar, 80 °C) affording 3.51 g of **36d**; m.p. 96–100 °C. ^{1}H NMR (250 MHz, $CDCl_3$): 1.34 (s, 2 CH_3)$_3$C); 2.32 (s, CH_3CO); 3.78 (s, OCH_3); 6.87 (s, 2 H-arom.).

*(3R)-3-Hydroxy-5-methylhexanoic acid (**37**); general procedure*

To a solution of diisopropylamine (0.51 g, 5.04 mmol) in dry Et_2O (10–20 ml), n-BuLi (4.4 mmol, 1.4–1.6 M in hexane) was added at r.t. (Ar). After cooling to −74 °C, tert-butyl acetate (**36e**, 440 mg, 3.79 mmol) was added by syringe and the mixture was stirred for 45 min at −74 °C. A solution of the Ti complex (5 mmol) in 120–160 ml of Et_2O was cooled to −74 °C and transferred via canula to the solution of enolate **39** within 30 min, using Ar pressure. The mixture was stirred for 30 min at −78 °C, 3 h at −30 °C using a cryostat, and recooled to −74 °C, before isovaleraldehyde (326 mg, 3.78 mmol) was added by syringe. After stirring for 2 h at −74 °C, 45% aq. NH_4F (20 ml) was added, and the mixture was stirred overnight at r.t. After filtration through Celite®, sat. NaCl solution was added, and the aqueous phase was separated and extracted with Et_2O (2×250 ml). The organic phases were washed with 1 N HCl, 10% $NaHCO_3$ solution, and sat. NaCl, dried (Na_2SO_4) and evaporated. The residue, ligand and tert-butyl (3*R*)-3-hydroxy-5-methylhexanoate (**38e**), was treated with 2 N NaOH (6 ml) and CH_3OH (12 ml) at 50 °C, until TLC analysis (hexane/EtOAc = 4:1) showed complete saponification (2 h). After evaporation of CH_3OH, the mixture was extracted with Et_2O (2×50 ml). The organic phase, containing the chiral ligand, was washed with 2 N NaOH (25 ml). The combined aqueous phases were acidified to pH 1 with conc. HCl and extracted with EtOAc (3×100 ml). The organic layer was washed with sat. NaCl, dried with $MgSO_4$ and evaporated. An analytical sample (10 mg) of the residue, crude acid **37**, was derivatized with *N*-isopropyl-isocyanate according to the general procedure, and analyzed by capillary GLC (Chirasil-Val [20], carrier 90 kPa, 190 °C): (3*S*)-**37**, t_R = 9.35 min; (3*R*)-**37**, t_R = 9.58 min. Physical data of (*R*)-**37**: see ref. 14b.

A. With cyclopentadienyl[(4R,trans)-2,2-dimethyl-α,α,α′,α′-tetraphenyl-1,3-dioxolane-4,5-dimethanolato-O(α),O(α′)]chlorotitanium ((R)-2)

(*a*) *Using tert-butyl acetate (**36e**).* The Li enolate **39**, prepared from t-butyl acetate (**36e**, 2.18 g, 18.77 mmol), was transmetalated with (*R*)-**2** [12] (15.33 g, 25 mmol) according to the general procedure (30 min at −78 °C, 3 h at −30 °C). Reaction with isovaleraldehyde (1.62 g, 18.8 mmol, 2 h at −78 °C) and saponification of the ester **38e** gave 11.3 g (96%) of ligand **33** and 2.6 g (95%) of crude acid (*R*)-**37** (78% e.e.). Crystallization from cyclohexane afforded 1.891 g (69%) of (*R*)-**37** (91% e.e.), recrystallization of which yielded 1.649 g (60%) of (*R*)-**37** (98% e.e.); $[\alpha]_D$ = −14.7 (c = 1, $CHCl_3$).

(*b*) *Using methyl acetate (**36a**).* The Li enolate **39**, prepared from methyl acetate (**36a**, 445 mg, 6 mmol), was transmetalated with (*R*)-**2** [12] (4.9 g, 8 mmol) according to the general procedure (24 h at −78 °C, 2 h at 0 °C). Reaction with isovaleraldehyde (517 mg, 6 mmol, 2 h at −78 °C) and saponification of the ester **38a** in analogy to the tert-butylester **38e** gave 342 mg (39%) of crude acid (*R*)-**37** (62% e.e.).

(*c*) *Using ethyl acetate (**36b**).* The Li enolate **39**, prepared from ethyl acetate (**36b**, 529 mg, 6 mmol), was transmetalated with (*R*)-**2** [12] (4.9 g, 8 mmol) according to the general procedure (1 h at −78 °C, 1 h at −30 °C, 1 h at 0 °C). Reaction with isovaleraldehyde (517 mg, 6 mmol, 2 h at −78 °C) and saponification of the ester **38b** in analogy to the tert-butylester **38e** gave 900 mg (quant.) of crude acid (*R*)-**37** (63% e.e.).

(*d*) *Using 2,4-dimethyl-3-pentyl acetate (**36c**).* The Li enolate **39**, prepared from **36c** (790 mg, 4.99 mmol), was transmetalated with (*R*)-**2** [12] (4.1 g, 6.7 mmol) according to the general procedure (1 h at −78 °C, 2 h at 0 °C). Reaction with isovaleraldehyde (431 mg, 5 mmol, 2 h at −78 °C), workup as described in the general procedure and chromatography (400 g of silica gel, hexane/EtOAc = 10:1) afforded 1.16 g (95%) of ester **38c**; 69% e.e. according to capillary GLC (Chirasil-Val, carrier 50 kPa, 120 °C), after derivatization with *N*-isopropyl-isocyanate according to the general procedure; (*R*)-**38c**: t_R = 30.5 min; (*S*)-**38c**: t_R = 31.1 min. ^{1}H NMR (250 MHz, $CDCl_3$): 0.7–1.0 (5 signals, 3 (CH_3)$_2$CH); 1.21 (ddd, J = 15, 8 and 5) and 1.52 (ddd, J = 15, 9 and 5) (2H–C(4)); 1.7–2.0 (m, 3 (CH_3)$_2$C*H*); 2.43 (dd, J = 16 and 9) and 2.54 (dd, J = 16 and 4)

(2H–C(2)); 2.7–3.1 (b, OH); 4.1 (dddd, $J=9$, 8, 5 and 4, H–C(3)); 4.65 (t, $J=6.5$, CHO).

(*e*) *Using 2,6-di-tert-butyl-4-methoxyphenyl acetate* (***36d***). The Li enolate **39**, prepared from **36d** (1.39 g, 5 mmol), was transmetalated with (*R*)-**2** [12] (4.1 g, 6.7 mmol) according to the general procedure (1 h at −78 °C, 1 h at 0 °C). Reaction with isovaleraldehyde (431 mg, 5 mmol, 20 h at −78 °C), workup as described in the general procedure, trituration of the crude product with pentane (50 ml) and filtration of the precipitated ligand (**33**, 2.84 g, 90%) afforded 1.96 g of crude ester **38d**. A solution of approximately half of **38d** was dissolved in CH_3CN/H_2O (4:1, 16 ml), and 5.33 g (9.7 mmol) of $Ce(NH_4)_2(NO_3)_6$ were added at 0 °C. After 30 min at 0 °C a further 1.52 g (2.78 mmol) of $Ce(NH_4)_2(NO_3)_6$ were added. After 50 min, H_2O (50 ml) and Et_2O (50 ml) were added. The aqueous phase was separated and extracted with Et_2O (2×50 ml). The organic phase was extracted with 2 N NaOH (2×25 ml), and the NaOH extracts were acidified with 37% HCl. Extraction with EtOAc (2×150 ml), washing with sat. NaCl solution, drying ($MgSO_4$) and evaporation gave 312 mg (85%) of crude acid **37** (74% e.e.).

B. With cyclopentadienyl[(4R,trans)-2,2-dimethyl-α,α,α′,α′-tetra(pentafluoro)phenyl-1,3-dioxolane-4,5-dimethanolato-O(α),O(α′)]chlorotitanium ((R)-48)

The Li enolate **39**, prepared from t-butyl acetate (**36e**, 114 mg, 0.98 mmol), was transmetalated with (*R*)-**48** [12] (30 ml of an approximately 0.043 M stock solution in Et_2O, ~1.3 mmol) according to the general procedure (1 h at −78 °C, 3 h at −30 °C). Reaction with isovaleraldehyde (84 mg, 0.98 mmol, 2 h at −78 °C) and saponification of the ester **38e** gave 114 mg (79%) of crude acid (*R*)-**37** (64% e.e.).

C. With cyclopentadienyl[(4R,trans)-2,2,α,α,α′,α′-hexamethyl-1,3-dioxolane-4,5-dimethanolato-O(α),O(α′)]chlorotitanium ((R)-49)

The Li enolate **39**, prepared from t-butyl acetate (**36e**, 697 mg, 6.0 mmol), was transmetalated with (*R*)-**49** [12] (58 ml of an approximately 0.12 M stock solution in Et_2O, ≈7 mmol) according to the general procedure (30 min at −78 °C, 1 h at 0 °C). Reactions with isovaleraldehyde (689 mg, 8 mmol, 2 h at −78 °C) and saponification of the ester **38e** gave 594 mg (67%) of crude acid (*R*)-**37** (42% e.e.).

D. With pentamethylcyclopentadienyl[(4R,trans)-2,2,α,α,α′,α′-hexamethyl-1,3-dioxolane-4,5-dimethanolato-O(α),O(α′)]chlorotitanium ((R)-50)

The Li enolate **39**, prepared from t-butyl acetate (**36e**, 305 mg, 2.626 mmol), was transmetalated with (*R*)-**50** [12] (1.521 g, 3.5 mmol) according to the general procedure (30 min at −78 °C, 2 h at −30 °C). Reaction with isovaleraldehyde (226 mg, 2.624 mmol, 2 h at −78 °C) and saponification of the ester **38e** gave 313 mg (81%) of crude acid (*R*)-**37** (57% e.e.).

E. With cyclopentadienyl[(4R,trans)-α,α,α′,α′-tetraphenyl-1,3-dioxolane-4,5-dimethanolato-O(α),O(α′)]chlorotitanium ((R)-51)

The Li enolate **39**, prepared from t-butyl acetate (**36e,** 436 mg, 3.75 mmol), was transmetalated with (*R*)-**51** [12] (86 ml of an approximately 0.058 M solution in Et_2O, ≈5 mmol) according to the general procedure (1 h at −78 °C, 3 h at −30 °C, 1 h at 0 °C). Reaction with isovaleraldehyde (323 mg, 3.75 mmol, 2 h at −78 °C) and saponification of the ester **38e** gave 493 mg (90%) of crude acid (*R*)-**37** (68% e.e.).

F. With cyclopentadienyl[(4R,trans)-2,2,α,α,α′,α′-hexaphenyl-1,3-dioxolane-4,5-dimethanolato-O(α),O(α′)]chlorotitanium ((R)-52)

The Li enolate **39**, prepared from t-butyl acetate (**36e**, 296 mg, 2.55 mmol), was transmetalated with (*R*)-**52** [12] (46 ml of an approximately 0.073 M solution in Et_2O, ≈3.36 mmol) according to the general procedure (1 h at −78 °C, 3 h at −30 °C, 1 h at 0 °C). Reaction with isovaleraldehyde (220 mg, 2.55 mmol, 2 h at −78 °C) and saponification of the ester **38e** gave 308 mg (82%) of crude acid (*R*)-**37** (42% e.e.).

G. With cyclopentadienyl{(4R,trans)-α,α,α′,α′-tetraphenyl-spiro-[1,3-dioxolane-2,9′-(9H)-fluorene]-4,5-dimethanolato-O(α),O(α′)}chlorotitanium ((R)-53)

The Li enolate **39**, prepared from t-butyl acetate (**36e**, 436 mg, 3.75 mmol), was transmetalated with (*R*)-**53** [12] (64 ml of an approximately 0.078 M solution in Et_2O, ≈5 mmol) according to the general procedure (1 h at −78 °C, 3 h at −30 °C, 1 h at 0 °C). Reaction with isovaleraldehyde (323 mg, 3.75 mmol, 2 h at −78 °C) and saponification of the ester **38e** gave 334 mg (61%) of crude acid (*R*)-**37** (71% e.e.).

H. With cyclopentadienyl[(7R,trans)-α,α,α′,α′-tetramethyl-dibenzo-b,e-bicyclo[2.2.2]octane-7,8-dimethanolato-O(α),O(α′)]chlorotitanium ((R)-54)

The Li enolate **39**, prepared from t-butyl acetate (**36e**, 254 mg, 2.187 mmol), was transmetalated with crude (*R*)-**54** (obtained from 940 mg, 2.915 mmol ligand (*R*)-**62**) according to the general procedure (15 h at −30 °C, 3 h at 0 °C). Reaction with isovaleraldehyde (188 mg, 2.183 mmol, 2 h at −78 °C) and saponification of the ester **38e** gave 201 mg (63%) of crude acid (*R*)-**37** (39% e.e.).

I. With cyclopentadienyl[(7R,trans)-α,α,α',α'-tetraphenyl-dibenzo-b,e-bicyclo[2.2.2]octane-7,8-dimethanolato-O(α),O(α')]chlorotitanium ((R)-55)

The Li enolate **39**, prepared from t-butyl acetate (**36e**, 234 mg, 2.014 mmol), was transmetalated with crude (*R*)-**55** (obtained from 1.535 g, 2.69 mmol ligand (*R*)-**63**) according to the general procedure (3 h at −30 °C). Reaction with isovaleraldehyde (174 mg, 2.02 mmol, 2 h at −78 °C) and saponification of the ester **38e** gave 197 mg (67%) of crude acid (*R*)-**37** (50% e.e.).

tert-Butyl 1,1,3,3-tetramethyl-1,3-disilaazolidine-N-acetate (42b)

To a suspension of tert-butyl glycinate hydrochloride (14.0 g, 83.5 mmol) in CH_2Cl_2 (200 ml), Et_3N (44 ml, 32.01 g, 316 mmol) was added at 0 °C, followed by 1,2-bis(chlorodimethylsilyl)ethane (23.4 g, 108.7 mmol) dissolved in CH_2Cl_2 (100 ml). After stirring for 19 h at r.t., additional Et_3N (7 ml, 5.09 g, 50.3 mmol) and 1,2-bis(chlorodimethylsilyl)ethane (5.4 g, 25.1 mmol) were added. The mixture was washed with buffer (0.41 M Na_2HPO_4/0.28 M KH_2PO_4), H_2O, and sat. NaCl solution. The organic phase was dried (Na_2SO_4) and the solvent was evaporated. Distillation (60–63 °C, 0.02 mbar) of the residue gave 12.7 g (55%) of **42b**. ^{1}H NMR (360 MHz, $CDCl_3$): 0.0 (s, 2 $(CH_3)_2Si$); 0.7 (s, 2 CH_2Si); 1.40 (s, $(CH_3)_3CO$); 3.36 (s, 2H–C(2)).

Ethyl (2S,3R)-2-(tert-butoxycarbonylamino)-3-hydroxy-hexanoate (43a)

To a solution of *N*-cyclohexyl-*N*-isopropylamine (1.9 g, 13.45 mmol) in dry THF (60 ml), n-BuLi (7.6 ml of an approximately 1.6 M solution in hexane, 12.16 mmol) was added at −20 °C (Ar). After 20 min the solution was cooled to −78 °C and ethyl 1,1,3,3-tetramethyl-1,3-disilaazolidine-*N*-acetate (**42a**, 3.0 g, 12.2 mmol) was added, dissolved in THF (60 ml). The mixture was stirred for 1 h at −78 °C, before a solution of complex (*R*)-**2** [12] (161 ml of an approximately 0.083 M solution in Et_2O, 13.3 mmol) was added. After stirring at −78 °C for 43 h, the solution was transferred via canula to a solution of butyraldehyde (0.97 g, 13.45 mmol) in dry THF (15 ml), precooled to −78 °C. The mixture was stirred for 22 h at −78 °C and finally quenched by the addition of H_2O (1.5 ml). After warming to r.t., the Ti salts were removed by filtration and H_2O (24 ml)/AcOH (4.8 ml) was added to the filtrate. Stirring was continued for 2 h, before volatiles were removed by careful evaporation under reduced pressure at r.t. An analytical sample (5 mg) of the residue (ethyl (2*S*,3*R*)-2-amino-3-hydroxy-hexanoate) was treated for 2 h with $(CF_3CO)_2O$ in CH_2Cl_2, before analysis by capillary GLC [20a, c] (Chirasil-Val, carrier 50 kPa, 90−180 °C/+2 °C per min): (2*S*,3*R*)-enantiomer, t_R = 11.7 min (90.8%); (2*R*,3*S*)-enantiomer, t_R = 10.8 min (9.2%); 81.6% e.e. The remaining material was dissolved in Et_2O (250 ml) and extracted with 0.1 N HCl (3×100 ml). The aqueous phases were extracted with Et_2O (2×250 ml), adjusted to pH 4 with 1 N NaOH and concentrated at r.t. (vacuum) to ≈50 ml. After addition of dioxane (80 ml), $NaHCO_3$ (6.7 g) and di-tert-butyl dicarbonate (5.3 g, 24.3 mmol), the mixture was stirred for 15 h at r.t. Et_2O (250 ml) was added before washing with H_2O (2×250 ml) and sat. NaCl solution (2×250 ml). The aqueous phases were extracted with Et_2O (2×250 ml). Evaporation of the dried (Na_2SO_4) organic phases and chromatography (silica gel, hexane/EtOAc = 4:1) of the residue afforded 2.09 g (62%) of **43a**; $[\alpha]_D = -2.7$ (c = 1.1, EtOH). ^{1}H NMR (300 MHz, $CDCl_3$): 0.9–1.0 (m, 3 main peaks, 3H–C(6)); 1.3 (t, J = 7, CH_3CH_2O); 1.3–1.6 (m, 2H–C(5), 2H–C(4)); 1.47 (s, $(CH_3)_3CO$); 1.95 (d, J = 6, HO–C(3)); 4.05–4.15 (m, H–C(2)); 4.24 (q, J = 7, CH_3CH_2O); 4.2–4.35 (m, H–C(3)); 5.25 (broad d, J = 7, NH).

tert-Butyl (2S,3R)-2-(tert-butoxycarbonylamino)-3-hydroxy-hexanoate (43b)

The Li enolate prepared from **42b** (1.5 g, 5.48 mmol) was transmetalated with (*R*)-**2** [12] (105 ml of an approximately 0.063 M solution in Et_2O, 6.6 mmol) as described above for **42a** (21 h at −78 °C). Reaction with butyraldehyde (470 mg, 6.52 mmol, 23 h at −78 °C), workup, GLC analysis and N-derivatization as described above afforded 1.03 g (61%) of **43b** (94% e.e.); $[\alpha]_D = -10.4$ (c = 1.3, EtOH). ^{1}H NMR (250 MHz, $CDCl_3$): 0.85–1.0 (m, 3 main peaks, 3H–C(6)); 1.35–1.7 (m, 2H–C(5), 2H–C(4)); 1.44 and 1.48 (2s, 2 $(CH_3)_3CO$); 1.5–2.0 (b, HO–C(3)); 3.97–4.1 and 4.13–4.25 (2m, H–C(2), H–C(3)); 5.23 (broad d, $J \approx 9$, NH). MS (field desorption): m/e = 305 ($M^+ + 2$, 10%), 304 ($M^+ + 1$, 100%), 303 (M^+, 24%), 230 (94%), 202 (76%). *Anal.* Calc. for $C_{15}H_{29}NO_5$ (303.40): C, 59.38; H, 9.64; N, 4.62. Found: C, 59.4; H, 9.7; N, 4.7%.

Results and discussion

Cyclopentadienyl-dialkoxy-chlorotitanium complexes with monodentate ligands

Monocyclopentadienyltitanium complexes **7** with two identical alkoxy ligands are conveniently obtained from $CpTiCl_3$ (**8**) [21] and two equivalents of a chiral alcohol R*OH in Et_2O. The evolving HCl is thereby neutralized with Et_3N. The precipitated hydrochloride is removed by filtration and the resulting ethereal solutions of the moisture sensitive complexes **7** can be used directly for subsequent reactions. To test their potential for asymmetric synthesis, the allyltitanium derivatives **9** were prepared and brought to reaction with benzaldehyde

at −78 °C. Hydrolytic workup afforded 1-phenyl-3-buten-1-ol (**10**) in good yield and with variable enantiomeric ratio (Fig. 3). While most auxiliaries R*OH tested gave low to moderate induction, 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (diacetoneglucose, **11**) turned out to be the only really successful monodentate ligand discovered so far, affording (*R*)-**10** with 99% e.e. [11]. As a consequence this system was broadly varied, with the hope to elucidate the key structural features for asymmetric induction [34] (Fig. 3)**.

Replacement of the acetonide protection by the corresponding 3-pentanone or cyclohexanone derivatives **12** and **13**, as well as the use of trichloroacetaldehyde derived β-chlorallose (**14–16**) and α-chlorallose (**17–19**) acetals [35] had only a minor effect on the stereoselectivity of the corresponding reagents **9**, which yielded (*R*)-**10** of 74–90% e.e. The importance of the 5,6-dioxolane ring becomes more evident, when the results of the ester- or silyl-protected D-glucofuranose derivatives **20–22** or the D-xylose analogs **23–25** are considered. Re addition to give (*R*)-**10** is still favored, but the induction is much lower (40–80% e.e.). While the 60% (*S*)-preference with acetonide protected D-allofuranose **26** seems reasonable, the result of the L-idofuranose derived ligand **27**, 70% (*S*)-**10** (40% e.e.) is rather puzzling, as **27** is closely related to diacetoneglucose **11** (C(5)-epimer) [10a, 12]. A distinct difference between the successful ligand **11** and **26** or **27** is the stability of their complexes of type **7**. The bis-diacetoneglucose derivative **1** is much more stable, and could be analyzed by ^{1}H NMR and ^{13}C NMR, the diastereotopic relation of the two alkoxy ligands being reflected by two sets of resonance signals [11b]. This was not the case, when solutions of the complexes **7** derived from **26** or **27** were evaporated for NMR analysis [36]. The ^{1}H NMR and ^{13}C NMR spectra of **1** are, furthermore, unaffected by temperature variations over a broad range (−100 to +100 °C [11b]), pointing to conformational rigidity. Whether the conformation of **1** in the crystalline state [11b] is matching the conformation in solution, could, however, not be confirmed, neither by NOE measurements (^{1}H NMR [11b]), nor by forcefield calculations [10a].

Cyclopentadienyl-dialkoxy-chlorotitanium complexes with bidentate ligands

Under certain conditions the formation of cyclic complexes is favored for enthropic reasons. A further advantage of such chelates is the restriction of conformational freedom, often a prerequisite for efficient stereocontrol of the corresponding reagents. If cyclic cyclopentadienyl-dialkoxy-chlorotitanium complexes should be obtained from $CpTiCl_3$ (**8**) and chiral diols

**These experiments are not described in 'Experimental'.

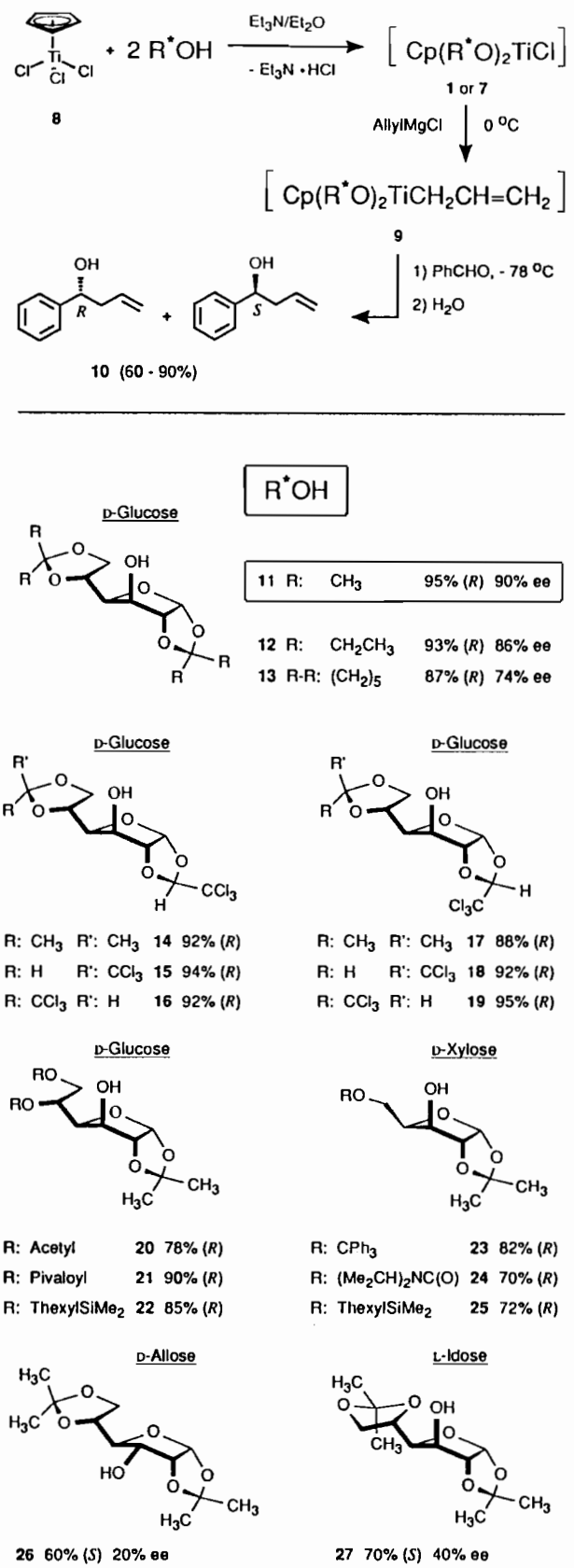


Fig. 3. Allyltitanation of benzaldehyde as test reaction for monodentate chiral ligands R*OH.

under thermodynamic control, the resulting titanacycles should be free of strain. According to a forcefield calculation based on Ti–O bond length, O–Ti–O and Ti–O–C(α) bond angles, obtained from the crystal structure of **1** [11b], the seven-membered ring is optimal [10a]. The 1,4-relation of hydroxy functions should therefore be chosen for such ligands, rather than 1,2- or 1,3-diols, which generally lead to complex polymeric or high nuclearity clusters (see ref. 9). Several chiral diols with C_2 symmetry were treated with $CpTiCl_3$ (**8**) and two equivalents of Et_3N in Et_2O or toluene at r.t. to 100 °C. After filtration from the precipitated hydrochloride, NMR analysis of the crude products was again a good method for assessing these conversions. In addition to distinct complexation shifts, doubling of most signals is a good indication for the formation of cyclopentadienylchlorotitanium derivatives, which lack C_2 symmetry. It turned out, that the geometrical constraints for the formation of monomeric and stable complexes are more severe than anticipated. Many promising ligands like binaphthol (**28**), D-mannitol bisacetonide (**29**), anhydromannitol (**30**) [37] and 1,3-dioxolane-4,5-dimethanol (**31**) [38] gave either mixtures of polymeric complexes or extremely sensitive derivatives, displaying only the ligand signals in the NMR (Fig. 4). It has, however, to be noted, that binaphthol (**28**) is a successful ligand for titanocenes [39], and that, in the absence of Cp ligands, **28** forms titanium complexes with a high tendency for aggregation [40], see ref. 9. Nevertheless, these rather ill-defined structures have been successfully applied as chiral Lewis acids for ene-reactions [6] and allylstannylations [8]. Remarkably stable monomeric cyclopentadienylchlorotitanium complexes, amenable to NMR and X-ray analysis, were, on the other hand, obtained from tetramethyl- and tetraphenyl-substituted 1,3-dioxolane-4,5-dimethanols (**32** and **33**) [12]. The 'Ingold-Thorpe-effect' [41] associated with the four alkyl substituents appears to be a prerequisite for the closure of titanacycles. The key pattern of successful 1,4-diol ligands with conformational fixation of the C(2)–C(3) bond and two tertiary alcohol functions is represented by the general formula **34**.

As mentioned in 'Introduction', complex (*R*)-**2** derived from ligand **33** [12, 5a, 30] is very successful for enantio- and diastereoselective allyltitanations of various aldehydes [12], but less efficient for aldol reactions [9, 10], which are described in full detail below (Fig. 5) and in 'Experimental'. While transmetalation with allylmagnesium chloride **35** and reaction with benzaldehyde gives (*S*)-**10** with 95% e.e. [12], addition of the Ti enolate derived from tert-butyl acetate **36e** gives the acid **37** via ester **38e** of 78% optical purity. In this specific case racemic **37** crystallizes as a conglomerate of enantiomers [14, 42]. Optically pure (*R*)-**37** can therefore be obtained by two recrystallizations of (*R*)-**37** of 78% e.e. (89% *R*) in 60% overall yield based

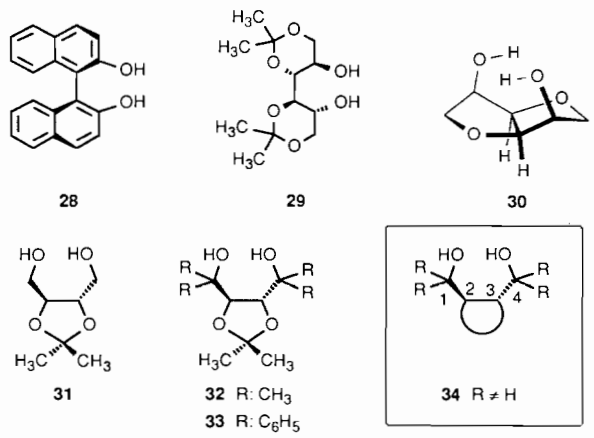


Fig. 4. Structures of 1,4-diol ligands successfully (**32–34**) and not successfully (**28–31**) applied for stereoselective monocyclopentadienyltitanium reagents.

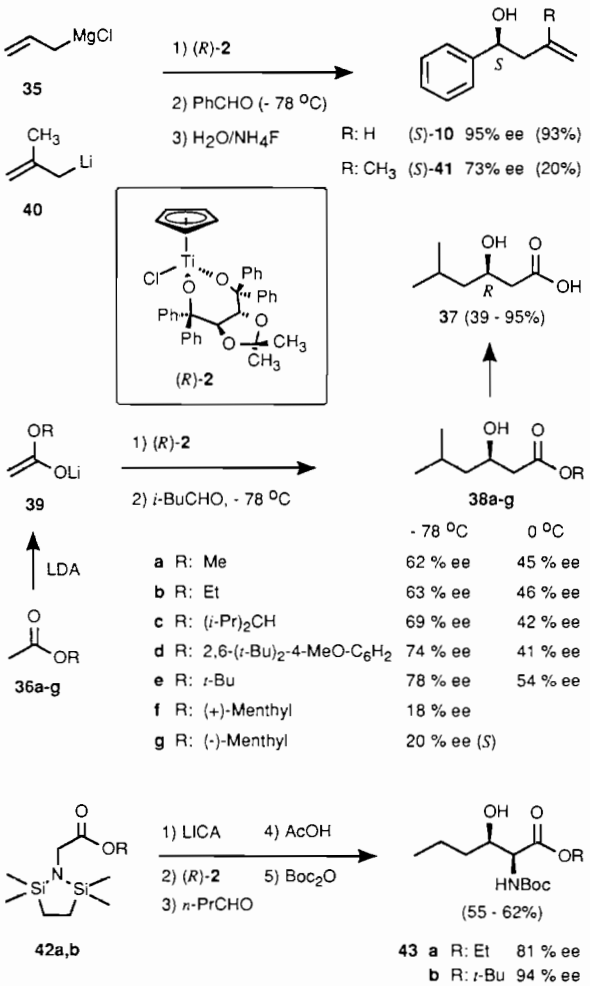


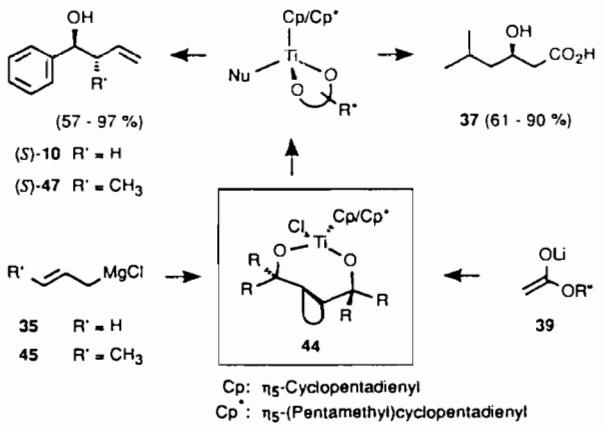
Fig. 5. Enantioselective allyltitanations and aldol reactions with complex (*R*)-**2**.

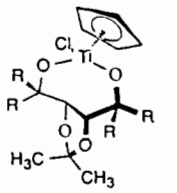
on **36e**. An obvious structural difference between the allyl-Grignard **35** and the enolate **39** is the ester substituent (OR) at the central atom of the 1,3-nucleophile. In line with such a substituent effect is the lower enantioselectivity of the methallyl reagent obtained by lithiation of isobutene (→**40**) with Li-2,2,6,6-tetramethylpiperidide/t-BuOK [43] and transmetalation with (*R*)-**2**, affording the benzaldehyde adduct **41** of 73% e.e. in low yield (20%)*. The effect of the ester group OR on the enantioselectivity of the acetate aldol reaction with (*R*)-**2** was, therefore, studied with **36a–e** (Fig. 5). Bulky esters led generally to higher enantiocontrol (69–78% e.e.) than methyl (62% e.e.) or ethyl (63% e.e.). The result with tert-butyl acetate (**36e**, 78% e.e.) could, however, not be improved with either 2,4-dimethyl-3-pentyl acetate (**36c**, 69% e.e.) or with 2,6-di-tert-butyl-4-methoxyphenyl acetate (**36d**, 74% e.e.) (see 'Experimental' for preparation of **36c** and **36d**). To ensure complete transmetalation, the Ti enolate solutions were split into two halves, one of which was treated at 0 °C with isovaleraldehyde (not described in 'Experimental'). The enantioselectivity was thereby reduced as predicted (41–54% e.e.), a good indication for a homogeneous Ti intermediate. This is another difference to the corresponding reaction of **36e**, transmetalated with the diacetoneglucose complex **1**, where the optical purity of (*S*)-**38e** (92–96% e.e.) was independent of the reaction temperature (−74 to +27 °C) [14]. In a different approach Rutledge and co-workers tried to improve the enantiocontrol by double asymmetric induction using (+)-menthyl and (−)-menthyl acetate (**36f** and **36g**) [44]. The low (*R*)-induction with **36f** (18% e.e.) and the reversal to (*S*)-preference with **36g** (20% e.e.) was tentatively explained by the steric bulk of these esters [44]. It has, however, to be kept in mind, that a comparison with our results is difficult, since these reactions were carried out in a different medium, THF/12-crown-4, instead of Et_2O (this work) or toluene [14].

Reaction of the Ti enolate derived from the stabase-protected glycine ethylester (**42a**) with butyraldehyde gives the L-threo-β-hydroxy-amino acid (**43a**) with 81% e.e., also a considerably lower induction, when compared with the diacetoneglucose system derived from **1**, affording the D-threo-enantiomer with 98% e.e. [16]. In this case, however, a useful result (94% e.e.) was obtained by increasing the size of the ester to tert-butyl (→**42b**) (see 'Experimental' for preparation). Unfortunately, better performance of α-substituted ester enolates is not general, and the aldol reactions of (*E*)- and (*Z*)-proprionate enolates proceed again with disappointing stereocontrol, when complex (*R*)-**2** is used as chiral template (26–78% e.e [9, 45]).

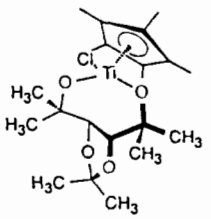
To evaluate effects on the enantioselectivity of the allyltitanation of aldehydes, several ligands of type **34** were converted to cyclopentadienyl-dialkoxy-chlorotitanium compounds of general structure **44**. These complexes were then used for the tansmetalation of allyl- or crotyl-Grignards (**35** and **45**, respectively), and the corresponding reagents **46** were tested by conversion of benzaldehyde to (*S*)-**10** and (*S*)-**47**, respectively [12]. In Fig. 6 these results are compared with the enantioselectivity of the Ti enolates, obtained from the same complexes **44** and **39**, in acetate aldol reactions with isovaleraldehyde, affording acid **37** after ester hydrolysis. With a few notable exceptions, the induction is generally higher for the allyl additions, and the aldol reaction appears to be less sensitive to ligand modifications, with enantioselectivities ranging from 39 to 78% e.e., as compared to the allyltitanation with inductions ranging from 5 to 95% e.e. While the drop in enantioselectivity associated with the pentafluorophenyl analog (*R*)-**48** is less pronounced for the aldol reaction, the β-hydroxy acid **37** prepared with the aid of the tetramethyl substituted complex (*R*)-**49** has a higher optical purity (42% e.e.) than the allyladduct (*S*)-**10** (12% e.e.) prepared with (*R*)-**49**. When the pentamethylcyclopentadienyl analog (*R*)-**50** is used, a dramatic increase of enantioselectivity is, however, observed only for the allylation (88% e.e.) and not for the aldol reaction (57% e.e.). Further ligand modifications consist in variations of the ring, used for fixation of the C(2)–C(3) torsion angle of the 1,4-diol system. For this purpose the acetonide of (*R*)-**2** has been replaced by a formaldehyde (→(*R*)-**51**), benzophenone (→(*R*)-**52**), and fluorenone acetal (→(*R*)-**53**). With the exception of the selectivity drop, observed for the aldol reaction with the benzophenone acetal system (*R*)-**52** (42% e.e.), the C(2) substituents of the dioxolane have only a moderate influence on the enantioselectivity. While the plane defined by the dioxolane substituents is perpendicular to the plane of the four substituents on the titanacycle, the two phenyl rings, annelated to the bicyclo[2.2.2]octane scaffold are parallel to this plane in the corresponding complexes (*R*)-**54** and (*R*)-**55** (see below for synthesis). It was therefore speculated, that the interaction of the benzannelated rings with the substituents R of (*R*)-**54** and (*R*)-**55** could have a marked effect on the stereoselectivity of the corresponding reagents. However, this turned out not to be the case, and only a somewhat lower induction was observed, when compared to (*R*)-**49** and (*R*)-**2**. A higher enantioselectivity for the aldol reaction, 39% e.e., when compared to the allyltitanation, (*S*)-**10** of 5% e.e., was

*Recent findings by Rutledge and co-workers [44] show, that combination of methallylmagnesium chloride and (*R*)-**2** is not at all successful. With the diacetoneglucose complex **1**, on the other hand, good results are reported with this Grignard precursor ((*R*)-**41** of 88% e.e) [44], while our experiments with **1** and methallyl-Li (**40**) gave (*R*)-**41** with 38% e.e. only (not described in 'Experimental').

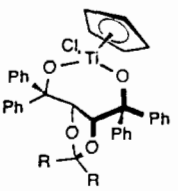




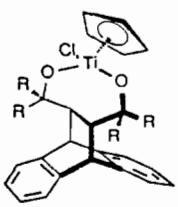
	Aldol	Allyl	
		R' = H	R' = CH_3
	(→ 37)	(→ (S)-10)	(→ (S)-47)
(R)-2 R: C_6H_5	78 % ee	95 % ee	98 % ee
(R)-48 R: C_6F_5	64 % ee	54 % ee	
(R)-49 R: CH_3	42 % ee	12 % ee	



	Aldol	Allyl
		R' = H
	(→ 37)	(→ (S)-10)
(R)-50	57 % ee	88 % ee



	Aldol	Allyl
		R' = H
	(→ 37)	(→ (S)-10)
(R)-51 R: H	68 % ee	80 % ee
(R)-52 R: C_6H_5	42 % ee	89 % ee
(R)-53 R: *spiro*-[9H]-fluorene	71 % ee	91 % ee



	Aldol	Allyl	
		R' = H	R' = CH_3
	(→ 37)	(→ (S)-10)	(→ (S)-47)
(R)-54 R: CH_3	39 % ee	5 % ee	19 % ee
(R)-55 R: C_6H_5	50 % ee	87 % ee	82 % ee

Fig. 6. Enantioselective allyltitanations and aldol reactions with Ti complexes of type **44**.

again observed for the methyl substituted complex (*R*)-**54**. The success of transmetalation can be reliably assessed with crotylmagnesium chloride (**45**), as the 1:1 *syn/anti* ratio obtained with Grignard reagent **45** turns into high *anti*-selectivity for the *trans*-crotyltitanium reagents. In the case of complexes (*R*)-**54** and (*R*)-**55** the *anti*-adduct (*S*)-**47** was isolated with 91% ds (19% e.e.) and 95% ds (82% e.e.), respectively.

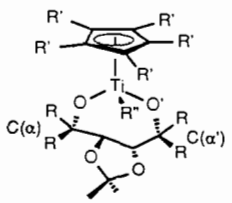
Crystal structure analyses and hypotheses for the mechanism of asymmetric induction

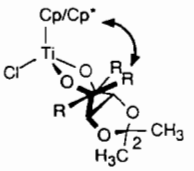
Some of the reagents derived from the cyclopentadienyl-dialkoxy-chlorotitanium complexes **1** and **2** (Fig. 1) are among the most stereoselective known [12, 14–16]. It is therefore highly desirable to understand their mechanism of enantioface discrimination. This must, however, be a formidable task, as the estimated $\Delta\Delta G^*$ needed for these inductions is less than 2 kcal/mol. Since the allyltitanation of benzaldehyde is more sensitive to structural changes, the following discussion is restricted to this process (see Fig. 6).

The bulk of the two pairs of geminal alkyl substituents display the most prominent influence on the enantioselectivity, with 95% e.e. for R = C_6H_5 ((*R*)-**2**) and 12% e.e. for R = CH_3 ((*R*)-**49**). A straightforward interpretation of this effect would relate the induction to an asymmetrical arrangement of these substituents around the reacting center, i.e. forming of an enzyme-like chiral cavity in direct relation to the bulk of these residues. While such an asymmetric environment was exhibited by the crystal structure of the diacetoneglucose complex **1** [11b], the four phenyl groups of (*R*)-**2** are oriented quite symmetrically around titanium [12]. Two of the bonds, attaching these phenyl groups, form a somewhat smaller angle (41 and 47° versus 73 and 62°) with a plane defined by C(α)–O–Ti–O–C(α'); i.e. two of the substituents, on opposite sides of this plane, are kind of axially oriented with respect to this plane, an argument which has been put forward by Seebach and co-workers for explaining the induction mechanism of various Ti complexes with such 'TADDOL' ligands [46] (see below, Fig. 10, for further discussion). Another plausible explanation involves a chiral distortion of the coordination geometry, resulting in a stereoelectronically governed induction by an asymmetrically hybridized metal center. This effect, leading to high enantioselectivity (98% e.e.), was demonstrated for an η_3-allyl–Mo complex in a pioneering study by Faller *et al.* [47]. Such an effect of distortion, which could be named 'enantiocontrol by convex asymmetry', as opposed to the notion 'concave' used for enzyme-like chiral cavities, could also be operative for these Ti reagents. The distortion could be caused by interactions of the cyclopentadienyl substituent with parts of the asymmetric ligands, i.e. one of the 5,6-dioxolane rings in the case of the di-

acetoneglucose system **1**, and the geminal R-substituents of the chelates **44** (see discussions in refs. 9, 10 and 12). This would then give a plausible explanation for the unexpected enantioselectivity enhancement (12% e.e. to 88% e.e.), observed upon replacing the Cp ligand of (*R*)-**49** by the larger pentamethyl Cp (→(*R*)-**50**) in conjunction with the tetramethyl substituted diol ligand (see Fig. 6). This hypothesis was sustained by the lineshape of the $^{47/49}$Ti NMR signals of **1**, (*R*)-**2** and (*R*)-**49** [12, 48], and was initially also related to different Ti–O–C(α) and Ti–O′–C(α′) bond angles displayed by the crystal structures of **1** and (*R*)-**2**, but not of (*R*)-**49** (see refs. 9 and 12]. In Fig. 7 these values are again listed together with the values for (*R*)-**50** [10b] and the μ-oxo dimer (±)-**56**.

Crystals of (*R*)-**50**, suitable for X-ray analysis, could finally be grown by slow evaporation of a toluene solution (see 'Experimental'). Two crystallographically different molecules, **A** and **B**, with different conformations were found in the crystal of (*R*)-**50**. ORTEP plots [33] and numbering of selected atoms are shown in Fig. 8. The μ-oxo dimer (*R*)-**56** is an impurity, often present in preparations of (*R*)-**2**, and it is also an intermediate of the hydrolysis of (*R*)-**2** and related derivatives. It can be prepared in high yield from (*R*)-**2** by controlled hydrolysis in the presence of base (Et_3N) or simply by shaking a solution of (*R*)-**2** in a non-water-miscible solvent with dilute aq. NaOH or 45% NH_4F. The dimer (*R*)-**56** is quite robust and can be chromatographed on





Complex			Angles [deg.] Detected by X-ray Diffraction		
			Ti-O-C(α)	Ti-O′-C(α′)	Cl-Ti-C(2)
1	(*Diacetoneglucose*)		145.8(8)	**153.1**(9)	
(*R*)-**2**	R: C_6H_5		**155.2**(6)	145.0(6)	103.4(5)
	R′: H				
	R″: Cl				
(*R*)-**49**	R: CH_3		148.6(7)	148.3(8)	**123.3**(5)
	R′: H				
	R″: Cl				
(*R*)-**50**	R: CH_3	Mol. A	143.7(6)	**149.7**(6)	103.0(1.0)
	R′: CH_3	Mol. B	145.6(6)	144.3(6)	100.0(1.0)
	R″: Cl				
(±)-**56**	R: C_6H_5	Ti(1)	**145.0**(1.0)	141.9(9)	107.9
	R′: H	Ti(2)	**142.3**(9)	137.6(8)	
	R″: $OTi(Cp)(OR^*)_2$	μ-oxo-dimer			

Fig. 7. Selected angles from X-ray crystal structure analyses.

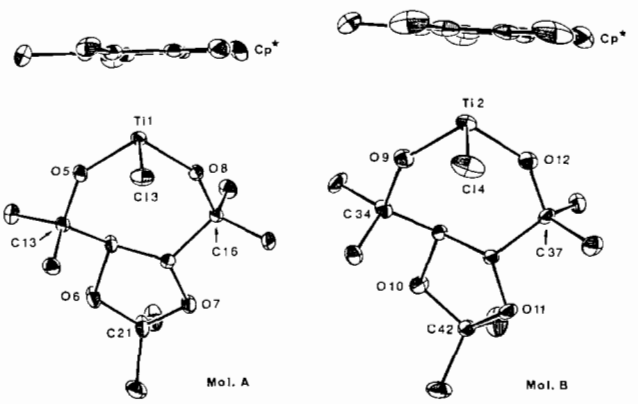
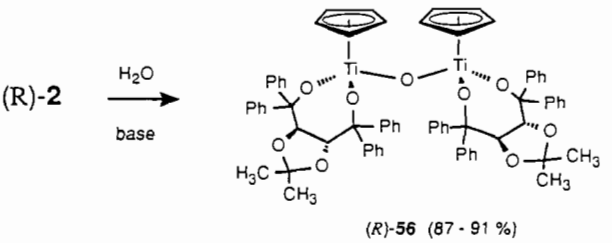


Fig. 8. ORTEP plot [33] and numbering of selected atoms of the crystal structure of (*R*)-**50**.



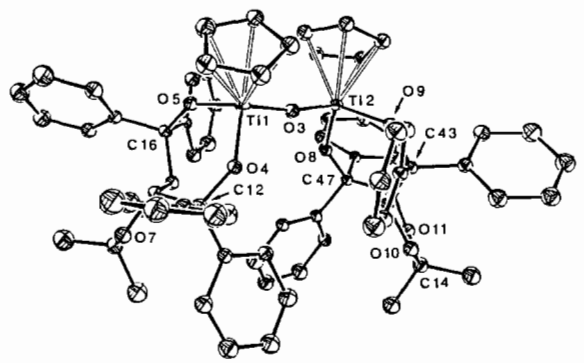


Fig. 9. Synthesis of (*R*)-**56** and ORTEP plot [33] with numbering of selected atoms of the crystal structure of (±)-**56**.

silica gel with non-protic solvents (Fig. 9). Due to its non-polar nature it is difficult to obtain crystals from pure enantiomers, e.g. (*R*)-**56**. Crystals suited for X-ray analysis could, however, be obtained easily from racemic (±)-**56**, prepared by mixing equimolar amounts of the enantiomers (*R*)-**56** and (*S*)-**56**. In $CDCl_3$ solution no ligand exchange of (±)-**56**, i.e. no evidence for the formation of the *meso*-dimer, could be observed up to 60 °C (^{1}H NMR). An ORTEP plot [33] of (±)-**56** is shown in Fig. 9. The two Cp rings point to the same side with a Cp^{center}–Ti(1)–Ti(2)–Cp^{center} angle of +49°. The Ti–O–Ti bond angle of 169° is typical for such μ-oxo-bridged Ti complexes [49]. The conformations of the two halfs of **56** are quite similar but not identical. Selected bond lengths, bond angles and torsion angles are listed in Table 2.

TABLE 2. Selected bond lengths, bond angles and torsion angles of structure (±)-**56**

Ti(1)		Ti(2)	
Bond lengths (pm)			
$Ti(1)–Cp^{center}$	209.1(3)	$Ti(2)–Cp^{center}$	207.2(3)
Ti(1)–O(3)	182.1(9)	Ti(2)–O(3)	181.5(9)
Ti(1)–O(4)	179.5(9)	Ti(2)–O(8)	180.2(9)
Ti(1)–O(5)	181.0(1.0)	Ti(2)–O(9)	182.0(1.0)
Bond angles (°)			
$Cp^{center}–Ti(1)–O(3)$	118.0(3)	$Cp^{center}–Ti(2)–O(3)$	116.8(4)
$Cp^{center}–Ti(1)–O(4)$	116.8(4)	$Cp^{center}–Ti(2)–O(8)$	118.5(4)
$Cp^{center}–Ti(1)–O(5)$	113.1(3)	$Cp^{center}–Ti(2)–O(9)$	111.6(3)
O(3)–Ti(1)–O(4)	103.0(4)	O(3)–Ti(2)–O(8)	103.8(4)
O(3)–Ti(1)–O(5)	105.0(5)	O(3)–Ti(2)–O(9)	105.2(5)
O(4)–Ti(1)–O(5)	98.4(5)	O(8)–Ti(2)–O(9)	98.7(5)
Ti(1)–O(4)–C(12)	145.0(1.0)	Ti(2)–O(8)–C(47)	142.3(9)
Ti(1)–O(5)–C(16)	141.1(9)	Ti(2)–O(9)–C(43)	137.6(8)
	Ti(1)–O(3)–Ti(2)	169.1(5.7)	
Torsion angles (°)			
$Cp^{center}–Ti(1)–O(3)–Ti(2)$	−47.8(3.8)	$Cp^{center}–Ti(2)–O(3)–Ti(1)$	−3.1(3.9)
Ti(2)–O(3)–Ti(1)–O(4)	−178.2(3.6)	Ti(1)–O(3)–Ti(2)–O(8)	−135.5(3.7)
Ti(2)–O(3)–Ti(1)–O(5)	+79.2(3.8)	Ti(1)–O(3)–Ti(2)–O(9)	+121.4(3.7)
$Cp^{center}–Ti(1)–O(4)–C(12)$	+91.3(1.6)	$Cp^{center}–Ti(2)–O(8)–C(47)$	+87.5(1.4)
$Cp^{center}–Ti(1)–O(5)–C(16)$	−159.4(1.3)	$Cp^{center}–Ti(2)–O(9)–C(43)$	−167.5(1.1)
C(12)–O(4)–Ti(1)–O(3)	−137.6(1.6)	C(47)–O(8)–Ti(2)–O(3)	−141.1(1.4)
C(12)–O(4)–Ti(1)–O(5)	−29.9(1.7)	C(47)–O(8)–Ti(2)–O(9)	−33.0(1.4)
C(16)–O(5)–Ti(1)–O(3)	+70.6(1.4)	C(43)–O(9)–Ti(2)–O(3)	+64.8(1.3)
C(16)–O(5)–Ti(1)–O(4)	−35.4(1.4)	C(43)–O(9)–Ti(2)–O(8)	−42.1(1.3)

Inspection of the data compiled in Fig. 7 clearly demonstrate that the enantiomeric angle distortion exhibited by the crystal structures of **1** and (*R*)-**2** cannot be used as a measure of a still possible chiral distortion related to the enantioface discrimination in the rate-determining transition state, the reason being that molecule **A** of structure (*R*)-**50** is distorted to the 'wrong' side, and that molecule **B** is quite symmetrical, resembling the non-enantioselective complex (*R*)-**49** with respect to these bond angles. The Ti–O–C(α) bond angles become smaller when the chloride of (*R*)-**2** is replaced by a μ-oxo bridge (complex (±)-**56**), but the distortion is retained and smaller. The influence of the Cp/Cp*–R interaction is, however, reflected by the angle formed by Cl, Ti and C(2) of the dioxolane ring. In the case of the complexes giving high asymmetric induction, (*R*)-**2** and (*R*)-**50**, the chelate ring is obviously pushed away from the Cp or Cp* group, resulting in a smaller value (100–103°, 108° for (±)-**56**), when compared to the 'unselective' complex (*R*)-**49**, with an angle of 123°.

Comparison of the X-ray structures of (*R*)-**2** and (±)-**56** reveals that the seven-membered 1,3-dioxa-2-titanacycles show quite different conformations. On top of Fig. 10 projections vertical to the C(α)–Ti–C(α') plane are displayed. For clarity the dioxolane rings are omitted. In the case of (*R*)-**2** the two ring oxygens (O(3) and O(4)) are also located on this plane and, as discussed above, the geminal phenyl substituents have different angles with this plane: 73°/41° for C(7) and 47°/62° for C(10). According to arguments used by Seebach *et al.* [46] this implies that the lower right front octant, the C(7) side, is more open for incoming reactants. In other projections, e.g. the lower part of Fig. 10 (see also refs. 9 and 12) this feature is, however, less distinct. Furthermore, crystal structures of conformationally mobile molecules might not display the conformer that is crucial for a certain property in solution. By replacing the chloride of (*R*)-**2** with a μ-oxo bridge (→(±)-**56**) a quite dramatic change of the conformation indicates indeed flexibility for these Ti chelates. As seen in Fig. 10 (top), the two oxygens (O(4) and O(5)) are turned counterclockwise out of the C(12)–Ti(1)–C(16) plane. The geminal phenyls still form different angles with this plane, but as the plane defined by Cp^{center}–Ti(1)–O(3) is not cutting vertically here, an approach from the right side, C(16), now appears to be more obstructed. This is also evident from the side-views displayed on the bottom of Fig. 10. While the phenyl substituents of (*R*)-**2** are arranged quite symmetrically and distant from Cl(2), one of the C(16) phenyls is protruding towards O(3) and even Ti(2) in the case of (±)-**56**. It is therefore conceivable that a 'conventional' chiral cavity in the rate-determining transition state might be responsible for the enantioselectivity involving these chiral Ti reagents.

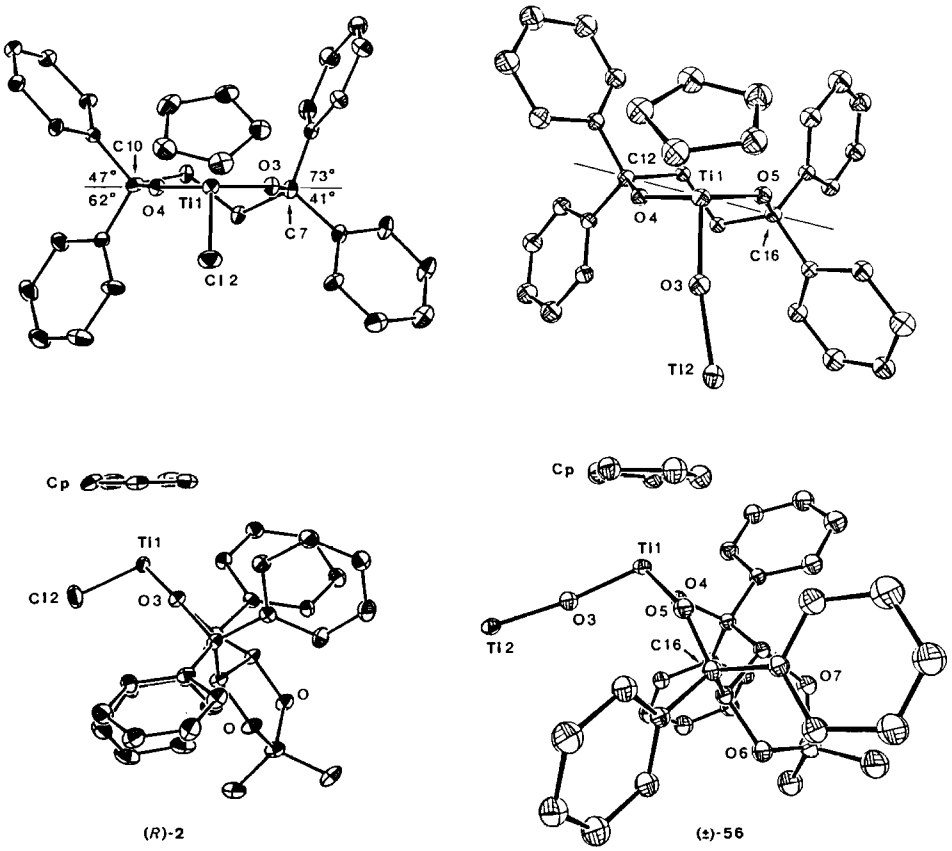


Fig. 10. Comparison of the conformations of complex (*R*)-2 and the Ti(1) moiety of (±)-**56** (X-ray).

As shown above (Fig. 7) the interaction between the cyclopentadienyl ligand and the four substituents on the α-carbons of the chelating 1,4-diol ligand has a marked influence on the complex conformation and also on the enantioselectivity of the allyltitanation and aldol reaction achieved with these chiral templates. In principle it should also be possible to influence the spatial arrangement of the two pairs of geminal substituents by interactions with the scaffold, used for the fixation of the C(2)–C(3) bond of the general ligand structure **34** (see Fig. 4). Replacement of the 2,2-disubstituted dioxolane ring of the TADDOL ligands by a dibenzo-*b*,*e*-bicyclo[2.2.2]octane should increase the rigidity, and the proximity of the annelated phenyl rings to the four substituents on the α-carbons could have an influence on the conformation of the Ti chelates derived from these novel ligands. The preparation of the complexes (*R*)-**54** and (*R*)-**55** was therefore envisaged (Fig. 11). Following the work of Helmchen and coworkers the (*R*,*R*)-configurated diester **57** was prepared with ethyl (*S*)-lactate **58** as chiral auxiliary [26]. The fumaric diester **59**, needed for the cycloaddition with anthracene, was prepared as described [25]; a side-product, the monoethyl ester **60**, could be separated by distillation. Transesterfication of **57** under carefully controlled conditions gave the dimethylester **61**, which could be transformed to the 1,4-diol ligands **62** and **63** by addition of Grignard reagents. Racemic **61**, **62** and **63** were obtained from racemic acid (±)-**64** [28] by esterification and Grignard addition. ^{1}H NMR analysis with the chiral shift reagent (+)-2,2,2-trifluoro-1-(9′-anthryl)ethanol (TFAE) [29], of the (*R*,*R*)-configurated samples of **61**, **62** and **63** showed no signals of the (*S*,*S*)-enantiomers, their enantiomeric purity was therefore ⩾95% e.e.

Reaction of (*R*)-**62** with $CpTiCl_3$ (**8**) proceeded smoothly without base by heating in toluene, affording the complex (*R*)-**54**, according to ^{1}H and ^{13}C NMR. The complexation with the sterically more crowded tetraphenyl analog (*R*)-**63**, on the other hand, was rather sluggish. Optimal conditions for ≈90% conversion to (*R*)-**55** consist in heating $CpTiCl_3$ (**8**) and (*R*)-**63** in toluene solution for 4 days and in the presence of Et_3N. This is a sharp contrast to the analogous chelates of dioxolane-dimethanol ligands, e.g. (*R*)-**2**, which form almost spontaneously. Despite this clear indication of steric congestion, the allyltitanations and aldol reactions with (*R*)-**54** and (*R*)-**55** showed a close analogy to the corresponding TADDOL chelates (*R*)-**49** and (*R*)-**2** (see above, Fig. 6). Enhancement of stereoselectivity for the

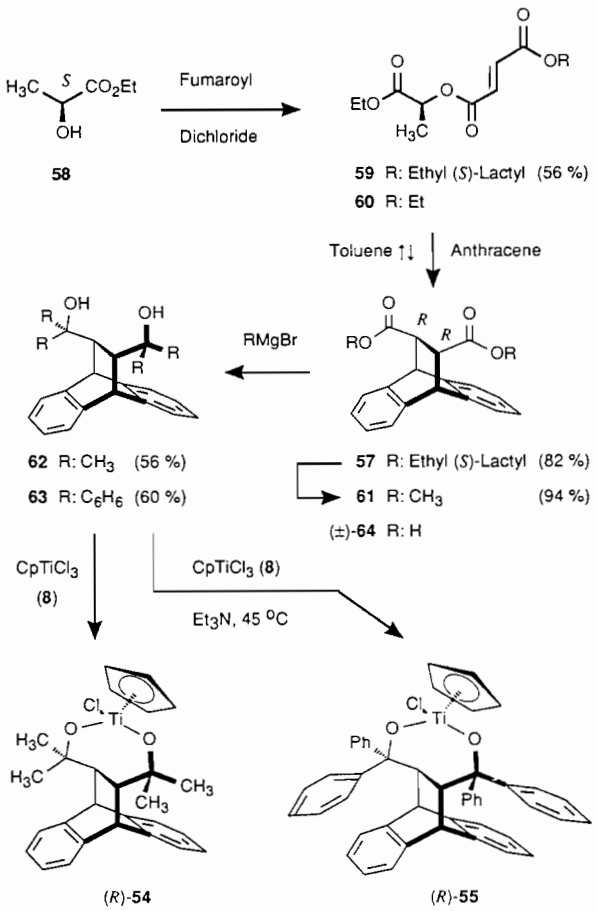


Fig. 11. Preparation of dibenzo-*b*,*e*-bicyclo[2.2.2]octane-7,8-dimethanol ligands and titanium complexes thereof.

$\alpha,\alpha,\alpha',\alpha'$-tetramethyl substituted systems can therefore only be effected by enlargement of the Cp ligand, i.e. by interligand strain, and not by intraligand interactions.

Supplementary material

Positional parameters of all atoms, thermal parameters, and observed and calculated structure factor amplitudes, as well as tables of bond distances and angles (crystal structure analyses) are available from the authors on request.

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