Synthesis of chiral polydentate ligands and the use of their titanium complexes as pre-catalysts for the asymmetric trimethylsilylcyanation of benzaldehyde

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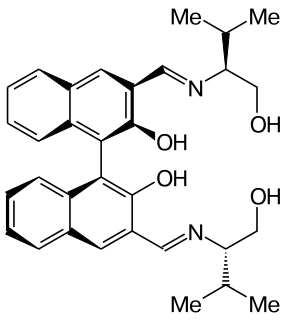
A number of polydentate ligands based on enantiomerically pure binaphthol have been synthesized. The ligand complexes with titanium isopropoxide were used as catalysts for the asymmetric addition of trimethylsilyl cyanide to benzaldehyde. A fragment with axial chirality is responsible for the configuration of *O*-trimethylsilyl cyanohydrin product. In the case of the optimum ligand based on (*R*)-binaphthol and (*S*)-leucinol, an enantiomeric excess of 86% and quantitative yield were achieved in 4 h.

Key words: asymmetric catalysis, titanium complexes, cyanohydrins, trimethylsilyl cyanide, benzaldehyde.

The role of asymmetric catalysis is difficult to overestimate. Nowadays, many pharmaceutical drugs are produced using chiral catalysts.[1] Despite the fact that the preparation and application of synthetic asymmetric catalysts is rapidly developing, as never before, only an insignificant portion of synthetic catalytic systems can compete with natural catalysts, enzymes, in activity or enantioselectivity.[1] A narrow substrate specificity, limited choice of solvents and reaction conditions can be considered as the disadvantages of enzyme catalysis.[1] It is obvious that development of synthetic asymmetric system possessing the advantages of the enzyme catalysts whilst lacking their disadvantages seems to be rather promising.

An important property of enzymes is that both the substrate and the reagent are simultaneously activated in their active center.[2] Note that many metalloenzymes contain two metal ions in their active center.[3—5] One of the reasons of such organization can be the mutual fixation and activation of two reagents in those centers. Earlier, we have reported on the development of highly efficient binuclear titanium(IV) complex obtained from the hexadentate ligand **1** and $Ti(OPr^i)_4$. The activity of such a binuclear catalyst considerably exceeds the activity of the mononuclear analog in terms of both TOF and stereodifferentiating ability.[6] The present work deals with a search for optimum substituents in ligand **1**.



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All the ligands were synthesized from (*R*)- or (*S*)-3,3′-diformyl-2,2′-dihydroxy-1,1′-binaphthyl ((*R*^{a})-**2** or (*S*^{a})-**2**) and the corresponding aminoalcohols or (*S*)-valine. Each enantiomer of dialdehyde **2** was obtained from the binaphthol **3** enantiomers (Scheme 1).

Aminoalcohols **6**—**11** were synthesized from the corresponding aminoacids by reduction (Scheme 2) or by reaction with the Grignard reagent (Scheme 3).

The condensation of dialdehydes **2** with 2 equiv. of aminoalcohols **6**—**11** led to the formation of the bis-Schiff bases **12**—**21** (Scheme 4).

The catalysts were obtained *in situ* by mixing the Schiff base with 2 equiv. of titanium isopropoxide. The molecular mass of complex **22**, obtained by the reaction of Schiff

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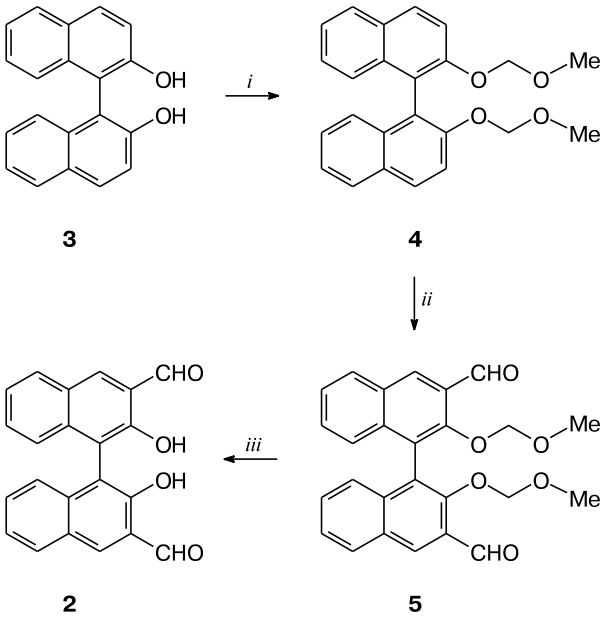
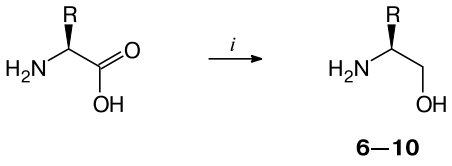
Scheme 1

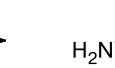


Reagents: *i*. 1) NaH/DMF, 2) MOMCl; *ii*. 1) BuLi/Et_2O, 2) DMF; *iii*. HCl/THF.

Scheme 2



i. $LiAlH_4$/THF.

R = Me (**6**), Bu^i (**7**), Bu^s (**8**), Bu^t (**9**),  (**10**)

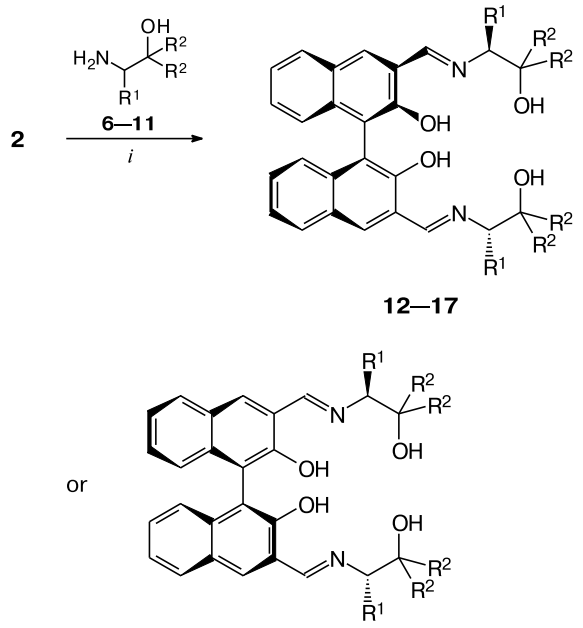
Scheme 3

i. PhMgBr/THF.

base **1** with a 2-fold excess of titanium isopropoxide, was determined by an ultracentrifugation method (see Experimental). It corresponded to the molecular mass of compound **22**, in which there were two fragments of the Schiff base **1** and four titanium atoms.

Attempted synthesis of a similar complex from (*S*)-valine and dialdehyde (R^a)-**2** was unsuccessful. In this case, it was impossible to incorporate more than one titanium molecule per binaphthol residue, however, even in this

Scheme 4

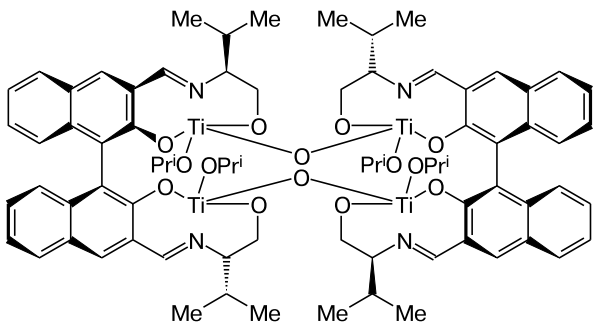


Compound	R^1	R^2	Compound	R^1	R^2
12, **18**	Me	H	**15**	Bu^t	H
13, **19**	Bu^i	H	**16**, **21**		H
14, **20**	Bu^s	H	**17**	H	Ph

i. Δ, benzene—ethanol.

case binuclear complex **23** was formed, as was confirmed by X-ray analysis (Fig. 1, Table 1).

Complex **23** crystallized as a solvate with two chloroform molecules. The titanium atoms in compound **23** are hexacoordinated. Their coordination polyhedron can be described as a distorted octahedron and a degree of distortion in the case of the Ti(1) atom is considerably higher, namely, the equatorial planes N(1), N(2′), O(1), O(2) and N(1′), N(2), O(1′), O(2′) are distorted by 0.004 and 0.12 Å, respectively. In addition to the change in degree of distortion of the coordination polyhedron, variation of the bond distances was also observed for the Ti(1) and Ti(2) atoms.



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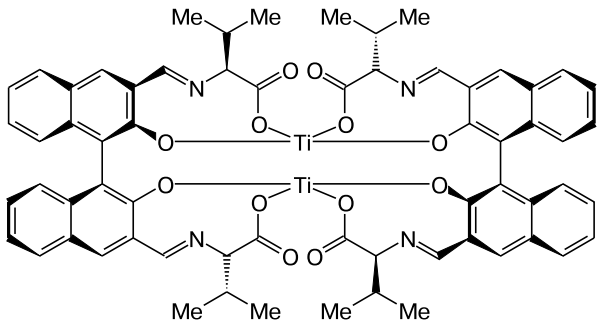

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The distortions and changes in geometry of the molecule observed are apparently caused by the steric overloading of the molecules. In fact, a shortened contact C(4)...C(4′) (3.301(1) Å) was observed for the two naphthalene rings in the complex, the length of which is considerably less than the sum of the van der Waals radii for carbon atoms. The geometries of two binaphthol ligands in compound **23** are close. In particular, the turning angle of two naphthalene ligands is 107.7 and 106.9°. In addition to steric factors, effects of crystal packing can also have an influence on the geometry of the complex. Both solvate molecules in the crystal form shortened contacts with the ester groups with the distances O...Cl being 2.924(1)—2.942(1) Å.

Despite the fact that the complex based on valine possessed catalytic activity, its stereodifferentiating ability turned out to be extremely low. During the standard time at +4 °C, mandelonitrile was formed in quantitative yield but in only 5% enantiomeric excess (Table 2, entry *15*).

When ligand **12** based on (*S*)-alaninol and (*R*)-binaphthol was used, formation of the product with (*R*)-configuration and enantiomeric purity of 68% was observed (see Table 2, entry *1*). In the case of ligand **18** differing only in configuration of the binaphthol fragment, product with enantiomeric purity of 58% but having (*S*)-configuration was obtained (see Table 2, entry *2*). To sum up, it is obvious that comparatively small size of the methyl group in diastereoisomers **12** and **18** has virtually no affect on the stereodifferentiating ability of the complexes on their basis with the configuration of the binaphthol fragment being the major factor determining the sign of asymmetric induction. An increase in the coordinating ability of the ligand on going from the Schiff bases **12** and **18** derived from alaninol to the Schiff bases **16** and **21** derived from phenylserinol (see Table 2, entries *3* and *4*) leads to a decrease in their catalytic activity and in the enantiomeric excess of (*R*)-mandelonitrile from 68 to 44%. In this case, the determining role of the configuration of the ligand binaphthol fragment for the sign of asymmetric induction of the catalyst is retained. The complex formed from (R^a,*S*,*S*)-Schiff base **16** leads to the formation of (*R*)-mandelonitrile, whereas the complex formed from (S^a,*S*,*S*)-isomer, to the (*S*)-product. The titanium complex of the Schiff base **17** formed from diphenylaminoethanol and (R^a)-**2** possessed still lower catalytic activity, giving during the standard time the product with (*R*)-configuration in 17% chemical yield and 27% *ee* (see Table 2, entry *5*). It is obvious that the introduction of bulky substituents at the β-position of the aminoalcohol hinders approach of the substrate and reagent to the reaction center of the catalyst, the metal ion.

Introduction of more bulky alkyl residues such as isobutyl (leucinol) and *sec*-butyl (*iso*-leucinol) leads to a considerable increase in asymmetric induction by the catalyst in comparison with alaninol derivatives. Thus, in the case

Table 1. Basic bond distances (*d*) in complex **23**

Bond	*d*/Å	Bond	*d*/Å
Ti(1)—O(1′)	1.860(5)	Ti(2)—O(1)	1.854(5)
Ti(1)—O(2′)	1.946(5)	Ti(2)—O(2)	1.985(6)
Ti(1)—O(4)	1.843(5)	Ti(2)—O(4′)	1.837(5)
Ti(1)—O(5)	1.926(5)	Ti(2)—O(5′)	1.908(5)
Ti(1)—N(1′)	2.181(6)	Ti(2)—N(1)	2.145(6)
Ti(1)—N(2)	2.172(6)	Ti(2)—N(2′)	2.159(6)

Table 2. Reaction of asymmetric addition of trimethylsilyl cyanide to benzaldehyde[a]

Entry	Ligand	Degree of conversion[b]	*ee*[c] (product configuration)
		%	
1	**12**	94	68 (*R*)
2	**18**	>99	58 (*S*)
3	**16**	88	44 (*R*)
4	**21**	56	18 (*S*)
5	**17**	17	27 (*R*)
6	**13**	>99	86 (*R*)
7	**14**	94	83 (*R*)
8	**19**	>99	37 (*S*)
9	**20**	>99	40 (*S*)
10	**15**	90	81 (*R*)
11	**1**	>99	86 (*R*)
12[d]	**13**	>99	38 (*R*)
13[e]	**13**	>99	5 (*R*)
14	**24**	>99	28 (*S*)
15	**23**[f]	>99	5 (*R*)

[a] Reaction conditions: 1—6 °C, CH_2Cl_2, 4 h, 10 mol.% of catalyst.
[b] Determined by ^1H NMR spectroscopy.
[c] Determined by GLC on a DP-TFA-γ-cD column (32 m × 0.20 mm), the absolute configuration was determined by comparison of the optical rotation angle of the product with the literature data.[7]
[d] Amount of the catalyst was 5 mol.%.
[e] Amount of the catalyst was 1 mol.%.
[f] Isolated complex was used.

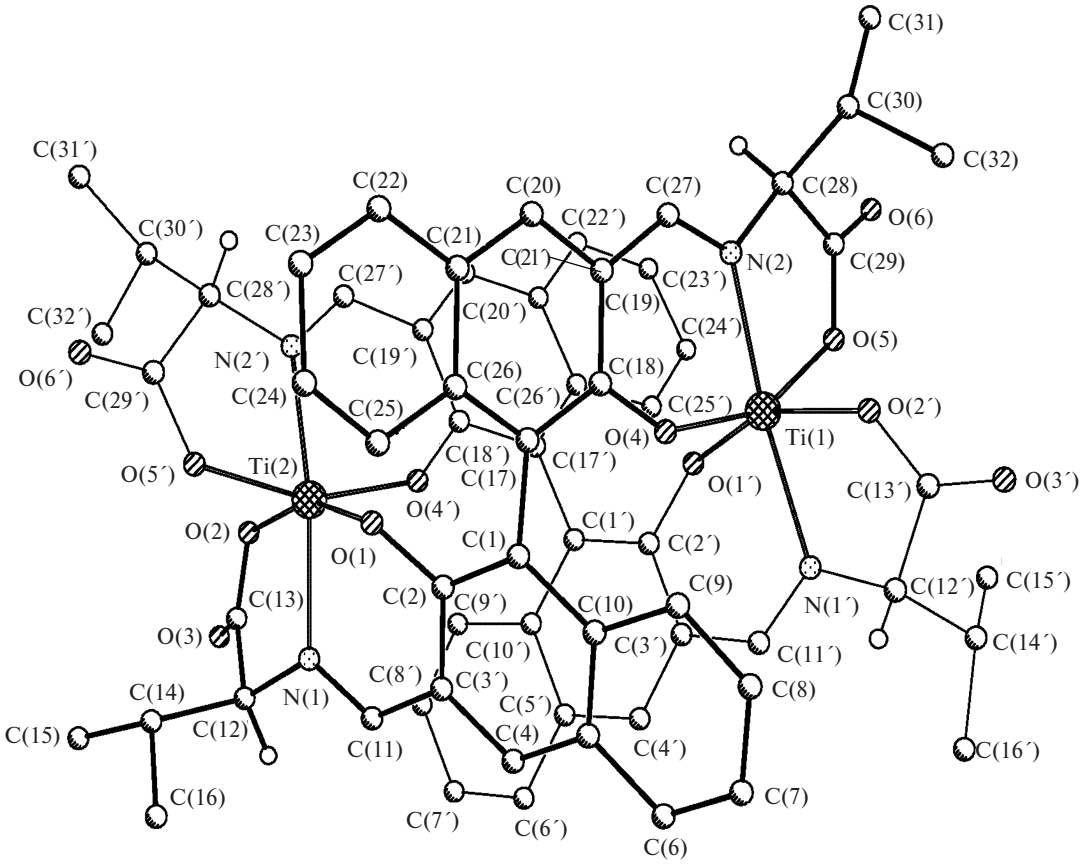
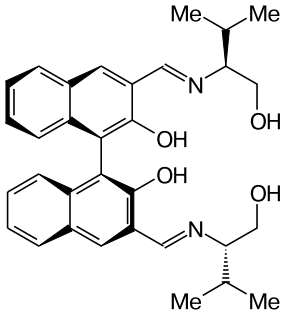


Fig. 1. General view of complex **23**.

of ligands **13** and **14**, the reaction product possessed an enantiomeric purity of 86 and 83% *ee*, respectively, with predominance of the product with (*R*)-configuration (see Table 2, entries *6* and *7*) as compared to 68% *ee* for the catalyst containing an alaninol residue (see Table 2, entry *1*). At the same time, for ligands **19** and **20** derived from (*S*)-binaphthol, a decrease in enantioselectivity of the process in comparison with the alaninol derivatives was observed. The enantiomeric excess of (*S*)-mandelonitrile decreased from 58% *ee* (see Table 2, entry *2*) to 37% *ee* (entry *8*) and 40% *ee* (entry *9*), however, even in these cases it was higher than for the valinol derivative **24** (entry *14*).



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Further increase in the size of the alkyl group to *tert*-butyl led to a decrease in the (*R*)-mandelonitrile *ee* to 81% (see Table 2, entry *10*). As can be seen from Table 2, the complexes derived from ligands **1** and **13**, giving the products in quantitative yield and enantioselectivity of 86%, possess the highest catalytic activity and stereodifferentiating ability among the catalysts presented (see Table 2, entries *6* and *11*). For the optimum catalyst derived from ligand **13**, experiments with lower amounts of the catalyst, *viz.*, 5 and 1 mol.%, respectively, have been carried out. It turned out that the catalyst did not lose its activity, but a sharp decrease in its stereodifferentiating ability, from 86 to 38 and 5%, respectively, occurred (see Table 2, entries *12* and *13*). This suggests that the real catalytic species possessing high asymmetric inducing ability is similar in its structure to tetranuclear species **22**. When the concentration of the pre-catalyst decreases, a dissociation of the tetranuclear species to the corresponding dititanium complexes takes place, which possess high catalytic activity, but have low stereodifferentiating ability.

Resulting conclusion, it was shown that the introduction of bulky substituents at the α-position of the aminoalcohol fragment causes a considerable decrease in the yield of the reaction products. An exchange of the aminoalcohol fragment for an aminoacid one leads to virtually entire loss

of enantiomeric purity of the product. It was found that the optimum ligands are **1** and **13**, in these cases a 86% enantiomeric excess and quantitative yield of the product can be reached in 4 h. Catalysts with other ligands possess lower stereodifferentiating ability.

Experimental

^1H and ^{13}C NMR spectra were recorded on a Bruker Avance 600 (600 MHz) and Bruker Avance 300 (300 and 75.5 MHz, respectively) spectrometers, chemical shifts were determined relative to the residual signal of undeuterated solvent. IR spectra were recorded on a UR-20 spectrometer in KBr pellets.

Optical rotations were determined on a Perkin—Elmer 241 polarimeter in a 5-cm incubatable cuvette at 25 °C. For all the compounds, the solvent and concentration (g per 100 mL of the solvent) are given.

Enantiomeric analysis of cyanohydrin trimethylsilyl ethers obtained was performed on a gas chromatograph (model 3700-00) using a DP-TFA-γ-cD chiral stationary phase (32 m × 0.20 mm). A racemic sample of each compound was used as the standard. Enantiomeric analysis of dialdehydes (R^a)-**2** and (S^a)-**2** was performed by HPLC using a Kromasil chiral stationary phase (0.46 cm × 25 cm, eluent: hexane—isopropanol, 100 : 4, 1 mL min^{-1}, UV detector, λ = 254 nm), $t_R(R)$ = 22.8 min, $t_R(S)$ = 20.8 min.

Elemental analysis was performed in the Elemental Analysis Laboratory of A. N. Nesmeyanov Institute of Organoelement Compounds of the Russian Academy of Sciences, prior to which the substances were heated *in vacuo* using a water-jet pump to 78 °C.

Commercial reagents (Aldrich or Acros) were used. Benzaldehyde and trimethylsilyl cyanide were distilled under argon at atmospheric pressure.

Introduction of methoxymethyl protection. (*R*)-2,2′-Bis(methoxymethoxy)-1,1′-binaphthyl ((*R*)-4). A solution of (*R*)-2,2′-binaphthol (4.87 g, 17 mmol) in DMF (50 mL) was added in small portions over 5 min to a stirred suspension of sodium hydride (2.88 g, 120 mmol) in DMF (50 mL) cooled in an ice-water bath. The reaction mixture was stirred under cooling for 30 min, then, methoxymethyl chloride (6 mL) was added in one portion. After 5 min, the ice-water bath was removed and additional portion of methoxymethyl chloride (0.8 mL) was added followed by stirring for 3 h at ~20 °C. Then, the reaction mixture was poured into water (400 mL) and extracted with ether (300 mL). The combined organic fractions were washed with water (4 times), saturated aqueous Na_2CO_3, and dried with anhydrous Na_2SO_4. The solvent was evaporated on a rotary evaporator at reduced pressure. The yellowish solid substance left was recrystallized from ethyl acetate to obtain the product (5.37 g, 84%) as white crystals, m.p. 99 °C. ^1H NMR ($CDCl_3$), δ: 3.15 (s, 6 H, Me); 4.99, 5.10 (both d, 2 H each, 2 CH_2, J = 6.7 Hz); 7.14—7.28 (m, 4 H, Ar); 7.36 (t, 2 H, Ar, J = 7.3 Hz); 7.59 (d, 2 H, Ar, J = 9.0 Hz); 7.88 (d, 2 H, Ar, J = 8.1 Hz); 7.96 (d, 2 H, Ar, J = 9.0 Hz). ^{13}C NMR ($CDCl_3$), δ: 55.8, 95.1, 117.2, 121.2, 124.0, 125.5, 126.3, 127.8, 129.4, 129.8, 134.0, 152.6.

(*S*)-2,2′-Bis(methoxymethoxy)-1,1′-binaphthyl ((*S*)-4) was obtained similarly from (*S*)-2,2′-binaphthol (4.87 g, 17 mmol), the yield was 5.3 g (83%), white crystals. ^1H NMR spectrum of compound (*S*)-**4** is similar to that of compound (*R*)-**4**; $[\alpha]_D^{25}$ −64.4 (*c* 1, THF).

Synthesis of dialdehydes (general procedure).[8] (*R*)-3,3′-Diformyl-2,2′-bis(methoxymethoxy)-1,1′-binaphthyl ((*R*)-5). Compound (*R*)-**4** (13.4 mmol) and anhydrous tetramethylethylenediamine (8 mL, 53 mmol) were dissolved in anhydrous ether (350 mL) under argon. The reaction mixture was cooled to 0 °C. A solution of butyllithium (1.6 *M*, 33 mL, 52.8 mmol) in hexane was added dropwise to the cold solution under argon over 10 min, the reaction mixture was stirred for 1 h at 0 °C. Then, anhydrous dimethylformamide (5 mL, 65 mmol) was added followed by additional stirring for 2 h at ~20 °C. After that, the reaction mixture was acidified to pH 5 by addition of 1 *M* aq. HCl. The organic layer was separated. The product was extracted from the water phase with ethyl acetate (3×100 mL), the combined organic fractions were washed with saturated aq. $NaHCO_3$, brine, and dried with Na_2SO_4. The yellow oil obtained after evaporation of the solvent was purified by column chromatography (hexane—ethyl acetate, 4 : 1). The yield was 4.1 g (72%), R_f 0.17. ^1H NMR ($CDCl_3$), δ: 2.87 (s, 6 H, Me); 4.69 (d, 2 H, CH_2, J = 6.6 Hz); 4.73 (d, 2 H, CH_2, J = 6.3 Hz); 7.22 (d, 2 H, Ar, J = 8.7 Hz); 7.42 (ddd, 2 H, Ar, J = 0.9 Hz, J = 7.5 Hz, J = 8.1 Hz); 7.52 (ddd, 2 H, Ar, J = 0.9 Hz, J = 6.9 Hz, J = 7.8 Hz); 8.08 (d, 2 H, Ar, J = 8.1 Hz); 8.62 (s, 2 H, Ar); 10.55 (s, 2 H, CHO). ^{13}C NMR ($CDCl_3$), δ: 57.0, 100.6, 125.9, 126.1, 126.3, 128.8, 129.6, 130.1, 130.3, 132.29, 136.7, 154.0, 190.6.

(*S*)-3,3′-Diformyl-2,2′-bis(methoxymethoxy)-1,1′-binaphthyl ((*S*)-5) was obtained similarly from compound (*S*)-**4** (5.0 g, 13.4 mmol). The yield was 4.0 g (69%), R_f 0.17. ^1H NMR spectrum of compound (*S*)-**5** is similar to that of compound (*R*)-**5**.

Removal of methoxymethyl protection.[9] (*R*)-3,3′-Diformyl-2,2′-dihydroxy-1,1′-binaphthyl ((*R*^{a})-2). Compound (*R*)-**5** (4.76 mmol) was dissolved in THF (40 mL) and cooled in an ice-water bath. Then, HCl (12 *M*, 17 mL) was added over 5 min with stirring and the ice-water bath was removed. Formation of yellow precipitate was observed and the stirring was continued for 3 h at ~20 °C. Then, the product was extracted with ethyl acetate (7×40 mL). The organic phase was washed with water, saturated aq. $NaHCO_3$, and brine and dried with anhydrous Na_2SO_4. The solvent was evaporated on a rotary evaporator at reduced pressure to obtain the product as a yellow powder. The yield was 1.56 g (96%), m.p. 285 °C, $[\alpha]_D^{25}$ +249.5 (*c* 0.8, CH_2Cl_2) (*cf.* Ref. 9: $[\alpha]_D^{20}$ −254 (*c* 0.3, CH_2Cl_2) for (*S*)-enantiomer). ^1H NMR ($CDCl_3$), δ: 7.11—7.15 (m, 2 H); 7.32—7.36 (m, 4 H); 7.93—7.97 (m, 2 H); 8.31 (s, 2 H); 10.13 (s, 2 H, OH); 10.53 (s, 2 H, CHO), *ee* 98.8%.

(*S*)-3,3′-Diformyl-2,2′-dihydroxy-1,1′-binaphthyl ((*S*^{a})-2) was obtained similarly using compound (*S*)-**5**. The yield was 1.5 g (95%), $[\alpha]_D^{25}$ −267 (*c* 0.5, CH_2Cl_2) (*cf.* Ref. 8: $[\alpha]_D^{20}$ −254 (*c* 0.3, CH_2Cl_2)), *ee* 100%. ^1H NMR spectrum of compound (S^a)-**2** is similar to that of compound (*R*)-**2**.

Synthesis of aminoalcohols.[10] Aminoacid (0.085 mol) was carefully added in 20 portions to a suspension of lithium aluminum hydride (5 g, 0.131 mol) in anhydrous THF (100 mL) under argon at ~20 °C. The reaction mixture was refluxed for 16 h, cooled to ~20 °C, and poured into diethyl (or methyl *tert*-butyl) ether (100 mL). Further, water (15 mL), 15% aq. sodium hydroxide (15 mL), and water (45 mL) were sequentially added to the ethereal fraction. The solution was filtered, the precipitate was washed with ether (2×50 mL). The organic layers were combined and dried with anhydrous sodium sulfate. Pure aminoalcohol was obtained by distillation *in vacuo*.

(*S*)-Alaninol (6). The yield was 2 g (89%), $[\alpha]_D^{25}$ +36.6 (*c* 2, $CHCl_3$) (*cf.* Ref. 11: $[\alpha]_D^{25}$ +36.2 (*c* 2, $CHCl_3$)), b.p. 59—61 °C

(5 Torr) (*cf.* Ref. 12: b.p. 59—60 °C (5 Torr)). ^{1}H NMR ($CDCl_3$), δ: 1.03 (d, 3 H, Me, J = 6.45 Hz); 2.14 (br.s, 3 H, NH_2, OH); 2.92—3.01 (m, 1 H, C<u>H</u>(Me)); 3.21 (dd, 1 H, C<u>H</u>(CH_2), J = 7.7 Hz, J = 10.7 Hz); 3.51 (dd, 1 H, C<u>H</u>(CH_2), J = 3.5 Hz, J = 10.2 Hz).

(*S*)-Leucinol (7). The yield was 2.98 g (85%), $[\alpha]_D^{25}$ +4.3 (*c* 0.9, EtOH) (*cf.* Ref. 13: $[\alpha]_D^{25}$ +4.2 (*c* 0.9, EtOH)), b.p. 92—94 °C (5 Torr) (*cf.* Ref. 14: b.p. 73—74 °C (1.4 Torr)). ^{1}H NMR ($CDCl_3$), δ: 0.9, 0.93 (both d, 3 H each, Me, J = 6.66 Hz); 1.18 (t, 2 H, CH_2, J = 6.99 Hz); 1.63—1.74 (m, 1 H, C<u>H</u>(Me)); 1.87 (br.s, 3 H, NH_2, OH); 2.86—2.94 (m, 1 H, C<u>H</u>NH_2); 3.21 (dd, 1 H, C<u>H</u>(CH_2O), J = 8.06 Hz, J = 10.42 Hz); 3.56 (dd, 1 H, C<u>H</u>(CH_2O), J = 3.88 Hz, J = 10.43 Hz).

(2*S*,3*S*)-2-Amino-3-methylpentan-1-ol (8). The yield was 2.9 g (84%), $[\alpha]_D^{25}$ +3.8 (*c* 1, EtOH) (*cf.* Ref. 15: $[\alpha]_D^{20}$ +3.5 (*c* 1, EtOH)), b.p. 88—90 °C (5 Torr) (*cf.* Ref. 16: b.p. 111—115 °C (20 Torr)). ^{1}H NMR ($CDCl_3$), δ: 0.79—0.86 (m, 6 H); 1.01—1.14, 1.26—1.35, 1.39—1.47 (all m, 1 H each); 2.57—2.63 (m, 4 H); 3.25 (dd, 1 H, J = 8.67 Hz, J = 10.59 Hz); 3.57 (dd, 1 H, J = 3.6 Hz, J = 10.65 Hz).

(*S*)-*tert*-Leucinol (9). The yield was 2.46 g (70%), $[\alpha]_D^{25}$ +36.5 (*c* 1.5, EtOH) (*cf.* Ref. 17: $[\alpha]_D^{25}$ +37 (*c* 1.5, EtOH)), b.p. 87—89 °C (5 Torr) (*cf.* Ref. 18: b.p. 65—70 °C (1.3 Torr)). ^{1}H NMR ($CDCl_3$), δ: 0.89 (s, 9 H, 3 Me); 1.71 (br.s, 3 H, NH_2, OH); 2.50 (dd, 1 H, J = 3.9 Hz, J = 10.2 Hz); 3.19 (t, 1 H, J = 10.2 Hz); 3.69 (dd, 1 H, J = 3.9 Hz, J = 10.2 Hz).

(1*S*,2*S*)-2-Amino-1-phenylpropane-1,3-diol (10). The yield was 1.44 g (90%), $[\alpha]_D^{25}$ +26.2 (*c* 10, MeOH) (*cf.* Ref. 19: $[\alpha]_D^{22}$ +26.6 (*c* 10, MeOH)), m.p. 115—117 °C. ^{1}H NMR ($CDCl_3$), δ: 1.99 (br.s, 4 H); 3.00 (q, 1 H, J = 5.41 Hz, J = 10.04 Hz); 3.55 (dd, 1 H, J = 5.98 Hz, J = 10.79 Hz); 3.65 (dd, 1 H, J = 4.22 Hz, J = 10.73 Hz); 4.65 (d, 1 H, J = 5.2 Hz); 7.29—7.32 (m, 1 H); 7.33—7.37 (m, 4 H). Aminoacid (*S*)-phenylserine used as the starting compound for the synthesis of aminoalcohol **9** was obtained according to the procedure described earlier.[20]

Synthesis of 2-amino-1,1-diphenylethanol (11). Glycine ethyl ester hydrochloride (1.4 g, 10 mmol) was slowly added to a solution of PhMgBr (1.0 mol L^{-1}, 60 mL, 60.0 mmol) in anhydrous THF (100 mL). The solution was stirred for 3 h at 40 °C and cooled to ~20 °C followed by addition of water (20 mL). The reaction mixture was diluted with ether (100 mL) and washed with brine. The water layer was extracted twice with diethyl ether—THF (3 : 2). The combined organic phases were washed with brine and dried with Na_2SO_4. After the solvent was evaporated on a rotary evaporator at reduced pressure, the residue was recrystallized three times from diethyl ether and purified by column chromatography (SiO_2; $CHCl_3$—MeOH, 8 : 2) to obtain the product (1.1 g, 52%) as white crystals, m.p. 112—114 °C (*cf.* Ref. 21: m.p. 110 °C). ^{1}H NMR ($CDCl_3$), δ: 2.80—3.20 (br.s, 3 H, NH_2, OH); 3.38 (s, 2 H, CH_2); 7.20—7.50 (m, 10 H, Ar).

Synthesis of the Schiff bases (general procedure). Dialdehyde (2.5 mmol) was added to a solution of aminoalcohol (5 mmol) in benzene (5 mL) and ethanol (5 mL). The reaction mixture was refluxed for 10 h with a Dean—Stark trap. The solvent was evaporated on a rotary evaporator at reduced pressure, the residue was purified by column chromatography on Sephadex LH-20 (dichloromethane). The Schiff bases were obtained as solid reddish orange compounds.

(*R*)-1-{2-Hydroxy-3-[((*S*)-2-hydroxy-1-methylethyl)imino]-methyl-1-naphthyl}-3-[((*S*)-2-hydroxy-1-methylethyl)imino]-methyl-2-naphthol (12). The yield was 1 g (95%, without residual solvent 87%), m.p. 136—138 °C, $[\alpha]_D^{25}$ −38.1 (*c* 1.05, $CHCl_3$). Found (%): C, 75.04; H, 6.39; N, 5.19. $C_{28}H_{28}N_2O_4 \cdot 0.5C_6H_6$. Calculated (%): C, 75.13; H, 6.30; N, 5.65. ^{1}H NMR ($CDCl_3$), δ: 1.22 (d, 6 H, J = 5.97 Hz); 1.87 (br.s, 2 H); 3.64 (m, 6 H); 7.18 (m, 2 H); 7.28—7.32 (m, 4 H); 7.87—7.90 (m, 2 H); 7.98, 8.69 (both s, 2 H each); 13.25 (br.s, 2 H). ^{13}C NMR ($CDCl_3$), δ: 18.2, 66.9, 116.6, 120.9, 123.5, 124.7, 127.6, 128.5, 128.9, 133.6, 135.3, 154.6, 165.3. IR, ν/cm^{-1}: 3369, 2926, 1632, 1254, 1042.

(*S*)-1-{2-Hydroxy-3-[((*S*)-2-hydroxy-1-methylethyl)imino]-methyl-1-naphthyl}-3-[((*S*)-2-hydroxy-1-methylethyl)imino]-methyl-2-naphthol (18). The yield was 1.1 g (97%, without residual solvent 90%), m.p. 128—130 °C, $[\alpha]_D^{25}$ −4.7 (*c* 1, $CHCl_3$). Found (%): C, 67.07; H, 5.84; N, 5.40. $C_{28}H_{28}N_2O_4 \cdot 0.65CH_2Cl_2$. Calculated (%): C, 67.24; H, 5.77; N, 5.47. ^{1}H NMR spectrum of compound **18** is similar to that of compound **12**. IR, ν/cm^{-1}: 3361, 2940, 1632, 1253, 1041.

(*R*)-1-{2-Hydroxy-3-([(1*S*,2*S*)-1-(hydroxymethyl)-2-methylbutyl]iminomethyl)-1-naphthyl}-3-([(1*S*,2*S*)-1-(hydroxymethyl)-2-methylbutyl]iminomethyl)-2-naphthol (14). The yield was 1.27 g (94%, without residual solvent 84%), m.p. 108—110 °C, $[\alpha]_D^{25}$ −146.7 (*c* 0.55, $CHCl_3$). Found (%): C, 69.88; H, 6.85; N, 4.55. $C_{34}H_{40}N_2O_4 \cdot 0.65CH_2Cl_2$. Calculated (%): C, 69.84; H, 6.99; N, 4.70. ^{1}H NMR ($CDCl_3$), δ: 0.83 (t, 6 H, J = 7.37 Hz); 0.91 (d, 6 H, J = 6.8 Hz); 1.11 (m, 2 H); 1.47 (br.s, 2 H); 1.64 (m, 4 H); 3.2 (m, 2 H); 3.75 (m, 4 H); 7.17 (m, 2 H); 7.29 (m, 4 H); 7.88 (m, 2 H); 7.99, 8.64 (both s, 2 H each); 13.18 (br.s, 2 H). ^{13}C NMR ($CDCl_3$), δ: 11.3, 15.7, 25.5, 36.9, 63.9, 116.6, 120.9, 123.4, 124.8, 125.02, 127.6, 128.6, 133.6, 135.3, 154.8, 166.03. IR, ν/cm^{-1}: 3405, 2945, 1633, 1255, 1045.

(*R*)-1-{2-Hydroxy-3-([(1*S*,2*S*)-1-(hydroxymethyl)-2-methylbutyl]iminomethyl)-1-naphthyl}-3-([(1*S*,2*S*)-1-(hydroxymethyl)-2-methylbutyl]iminomethyl)-2-naphthol (20). The yield was 1.26 g (93%, without residual solvent 80%), m.p. 110—112 °C, $[\alpha]_D^{25}$ −156.6 (*c* 0.76, $CHCl_3$). Found (%): C, 68.09; H, 7.06; N, 4.48. $C_{34}H_{40}N_2O_4 \cdot 0.88CH_2Cl_2$. Calculated (%): C, 68.07; H, 6.84; N, 4.55. ^{1}H NMR spectrum of compound **20** is similar to that of compound **24**. IR, ν/cm^{-1}: 3400, 2951, 1633, 1255, 1045.

(*R*)-1-{2-Hydroxy-3-([(*S*)-1-hydroxymethyl-2,2-dimethylpropyl]iminomethyl)-1-naphthyl}-3-([(*S*)-1-hydroxymethyl-2,2-dimethylpropyl]iminomethyl)-2-naphthol (15). Purification was performed by column chromatography on Sephadex LH-20 (dichloromethane—pyridine, 10 : 1). The yield was 1.27 g (94%, without residual solvent 68%), m.p. 160—162 °C, $[\alpha]_D^{25}$ −122.2 (*c* 0.55, $CHCl_3$). Found (%): C, 66.77; H, 7.01; N, 5.79. $C_{34}H_{40}N_2O_4 \cdot 1.2CH_2Cl_2 \cdot Py$. Calculated (%): C, 66.90; H, 6.62; N, 5.82. ^{1}H NMR ($CDCl_3$), δ: 0.91 (s, 18 H); 2.17 (br.s, 2 H); 3.00 (dd, 2 H, J = 2.27 Hz, J = 9.12 Hz); 3.67 (t, 2 H, J = 9.5 Hz); 3.69 (dd, 2 H, J = 2.2 Hz, J = 11.04 Hz); 7.14 (m, 2 H); 7.30 (m, 4 H); 7.87 (m, 2 H); 7.97, 8.63 (both s, 2 H each); 13.12 (br.s, 2 H). ^{13}C NMR ($CDCl_3$), δ: 27.1, 33.2, 62.1, 116.6, 120.8, 123.35, 125.03, 127.6, 128.1, 128.9, 133.6, 135.3, 154.7, 166.2. IR, ν/cm^{-1}: 2961, 3434, 1633, 1254, 1042.

(*R*)-1-{2-Hydroxy-3-([(*S*)-1-hydroxymethyl-2-methylbutyl]iminomethyl)-1-naphthyl}-3-([(*S*)-1-hydroxymethyl-2-methylbutyl]iminomethyl)-2-naphthol (13). The yield was 1.3 g (96%, without residual solvent 84%), m.p. 130—132 °C, $[\alpha]_D^{25}$ −135.3 (*c* 0.55, $CHCl_3$). Found (%): C, 68.69; H, 6.9; N, 4.3. $C_{34}H_{40}N_2O_4 \cdot 0.8CH_2Cl_2$. Calculated (%): C, 68.67; H, 6.89; N, 4.60. ^{1}H NMR ($CDCl_3$), δ: 0.88 (dd, 12 H, J = 5.32 Hz, J = 6.04 Hz); 1.26—1.33 (m, 2 H); 1.46—1.52 (m, 4 H); 2.06 (br.s, 2 H); 3.47 (m, 2 H); 3.58—3.64 (m, 4 H); 7.18 (m, 2 H);

7.30 (m, 4 H); 7.87 (m, 2 H); 7.99, 8.67 (both s, 2 H each); 13.21 (br.s, 2 H). ^{13}C NMR ($CDCl_3$), δ: 21.5, 23.5, 24.3, 40.8, 66.4, 70.1, 116.6, 120.8, 123.5, 124.8, 127.6, 128.5, 128.9, 133.7, 154.6, 165.8. IR, ν/cm^{-1}: 2196, 3400, 1632, 1255, 1063.

(*S*)-1-{2-Hydroxy-3-([(*S*)-1-hydroxymethyl-2-methylbutyl]-iminomethyl)-1-naphthyl}-3-([(*S*)-1-hydroxymethyl-2-methylbutyl]iminomethyl)-2-naphthol (19). The yield was 1.31 g (97%), m.p. 126—128 °C, $[\alpha]_D^{25}$ −143.2 (*c* 0.9, $CHCl_3$). Found (%): C, 75.24; H, 7.65; N, 4.95. $C_{34}H_{40}N_2O_4$. Calculated (%): C, 75.53; H, 7.46; N, 5.18. ^1H NMR spectrum of compound **19** is similar to that of compound **13**. IR, ν/cm^{-1}: 3050, 3400, 1632, 1256, 1060.

(*R*)-3-[(2-Hydroxy-2,2-diphenylethyl)imino]methyl-1-{2-hydroxy-3-[(2-hydroxy-2,2-diphenylethyl)imino]methyl-1-naphthyl}-2-naphthol (17). The yield was 1.7 g (93%, without residual solvent 73%), m.p. 112—114 °C, $[\alpha]_D^{25}$ +11.3 (*c* 0.7, $CHCl_3$). Found (%): C, 71.57; H, 5.42; N, 3.10. $C_{50}H_{40}N_2O_4 \cdot 1.5CH_2Cl_2$. Calculated (%): C, 71.90; H, 5.04; N, 3.26. ^1H NMR ($CDCl_3$), δ: 2.77 (br.s, 2 H); 4.38 (q, 4 H, J = 12.98 Hz); 7.09 (d, 2 H, J = 6.96 Hz); 7.19—7.30 (m, 16 H); 7.42—7.45 (m, 12 H); 7.83—7.86 (m, 2 H); 7.92, 8.64 (both s, 2 H each); 12.21 (br.s, 2 H). IR, ν/cm^{-1}: 2922, 3451, 1631, 1254, 1057.

(*R*)-2-{(3-Hydroxy-4-[2-hydroxy-3-([2-hydroxy-1-(hydroxymethyl)-2-(*S*)-phenylethyl]iminomethyl)-1-naphthyl]-2-naphthylmethylidene)amino}-1-(*S*)-phenyl-1,3-propanediol (16). The yield was 1.5 g (94%, without residual solvent 76%), $[\alpha]_D^{25}$ +93.8 (*c* 0.55, $CHCl_3$), m.p. 144—146 °C. Found (%): C, 68.75; H, 5.68; N, 3.98. $C_{40}H_{36}N_2O_4 \cdot 1.3CH_2Cl_2$. Calculated (%): C, 68.98; H, 5.41; N, 3.90. ^1H NMR ($CDCl_3$), δ: 2.77 (br.s, 4 H); 3.54 (m, 6 H); 4.8 (d, 2 H, J = 6.57 Hz); 7.16 (m, 2 H); 7.28—7.32 (m, 14 H); 7.86 (m, 2 H); 7.93, 8.69 (both s, 2 H each); 13.01 (br.s, 2 H). ^{13}C NMR ($CDCl_3$), δ: 63.0, 74.2, 116.6, 120.7, 123.5, 124.97, 126.6, 127.5, 127.8, 128.3, 129.1, 133.9, 135.3, 140.8, 154.6, 167.9. IR, ν/cm^{-1}: 3030, 2922, 1632, 1254, 1027.

(*S*)-2-{(3-Hydroxy-4-[2-hydroxy-3-([2-hydroxy-1-(hydroxymethyl)-2-(*S*)-phenylethyl]iminomethyl)-1-naphthyl]-2-naphthylmethylidene)amino}-1-(*S*)-phenyl-1,3-propanediol (21). The yield was 1.55 g (97%, without residual solvent 79%), $[\alpha]_D^{25}$ +252.2 (*c* 0.7, $CHCl_3$), m.p. 144—146 °C. Found (%): C, 70.07; H, 5.99; N, 4.08. $C_{40}H_{36}N_2O_4 \cdot 1.1CH_2Cl_2$. Calculated (%): C, 70.30; H, 5.48; N, 3.99. ^1H NMR spectrum of compound **21** is similar to that of compound **16**. IR, ν/cm^{-1}: 3030, 2922, 1632, 1254, 1027.

Complex 22. Titanium(IV) isopropoxide (11.4 μL, 39.0 μmol) was added to a solution of ligand **1** (10.0 mg, 19.5 μmol) in dichloromethane-d_2 (0.5 mL). In the ^1H NMR spectrum, many weak signals for other complexes are present in addition to the signals for the major product. ^1H NMR (CD_2Cl_2), δ: 0.87, 1.01 (both d, 6 H each, J = 6.7 Hz); 1.22—1.30 (br.d, 12 H, J = 4.2 Hz); 2.45 (m, 2 H); 3.47 (dd, 2 H, J = 4.2 Hz, J = 9.9 Hz); 3.60—3.80, 4.40—4.48 (both m, 2 H each); 4.58 (dd, 2 H, J = 4.2 Hz, J = 9.9 Hz); 7.00—7.40 (m, 6 H); 7.80—8.00 (m, 2 H); 8.08, 8.59 (both s, 2 H each).

Complex 23. Dialdehyde (R^a)-**2** (50.0 mg, 0.146 mmol) was added to a solution of (*S*)-valine (34.0 mg, 0.292 mmol) in benzene (5 mL) and isopropanol (5 mL). The reaction mixture was refluxed for 1 h with a Dean—Stark trap followed by addition of titanium(IV) isopropoxide (86 μL, 0.292 mmol) and refluxing with a Dean—Stark trap for another 10 h. The solvent was evaporated on a rotary evaporator at reduced pressure, the residue was purified by column chromatography on Sephadex LH-20 (dichloromethane). Complex **23** was obtained as a red powder. The complex was recrystallized from chloroform. The yield was 30 mg (15% with subtraction of two solvate chloroform molecules).

Catalytic asymmetric addition of trimethylsilyl cyanide to benzaldehyde (general procedure). Titanium(IV) isopropoxide (28 μL, 94 μmol) was added to a solution of a ligand (47 μmol) in dichloromethane (1 mL) under argon. The color of the solution changed instantly from orange to reddish brown. The reaction mixture was stirred for 2 h at ~20 °C followed by addition of freshly distilled benzaldehyde (48 μL, 471 μmol). The solution was cooled to +1 °C followed by addition of trimethylsilyl cyanide (100 μL, 750 μmol). The reaction mixture was stirred for 4 h at 4 °C and purified by column chromatography on SiO_2 (eluent, hexane—ethyl acetate, 5 : 1). The product was analyzed by ^1H NMR spectroscopy. The spectra obtained agreed with analogous spectra described earlier.[22] The chemical yield was calculated from the correlation of signals for the product and for the starting aldehyde. The enantiomeric composition was determined using gas chromatography on a DP-TFA-γ-cD column (32 m × 0.20 mm), the absolute configuration was determined by comparison of the optical rotation angle of the product obtained with the data in Ref. 7.

Measurement of molecular mass of complex 22 in dichloromethane. The molecular characteristics of titanium complex **9** were studied by the sedimentation equilibrium method in an analytical ultracentrifuge (MOM-3180). The molecular mass M_w for two samples was determined from the sedimentation data using the method of established equilibrium for concentrations of 0.5—1.0 g dL^{-1} (with the use of Fillpot—Swenson optics, the rotor temperature was 25±0.1 °C, the rotational velocity of the rotor was 50000 rpm). The apparent molecular mass for the finite concentrations was calculated by the following formula

$$M_w^{app} = \{RT/[(1 - V\rho_0)\omega^2]\}[(dc/dx)/(cx)],$$

where R is the universal gas constant, T is the absolute temperature (K), V is the partial specific volume of the substance, ρ_0 is the solvent density (dichloromethane) (g dL^{-1}), ω is the angular velocity of the rotor rotation, c is the concentration of the substance in solution, x is the distance from the axis of rotation (cm).

The true value of M_w was found by extrapolation of $1/M_w^{app}$ (determined for the finite concentrations) to the infinite dilution ($C \to 0$). The specific partial volume (V = 0.337 cm^3 g^{-1}) and the solvent density (ρ_0 = 1.3113 g cm^{-3} at 25 °C) necessary for the calculation of molecular mass from the sedimentation data were determined pyknometrically. The pyknometer was calibrated with respect to mercury. The value M_w = 1430±5%.

X-ray study. Crystals **23** ($C_{66}H_{58}Cl_6N_4O_{12}Ti_2$) at 100 K are monoclinic, a = 10.0376(12) Å, b = 18.579(2) Å, c = 17.159(2) Å, β = 90.307(4)°, V = 3199.9(7) Å^3, d_{calc} = 1.461 g cm^{-3}, space group $P2_1$, Z = 4. Intensities of 17701 reflections were measured on a Bruker Smart APEX II CCD automatic difractometer at 100 K (Mo-Kα irradiation, graphite monochromator, ω-scanning, $2\theta_{max}$ = 54°) and 9358 observed reflections were used in further calculations. The structure was decoded by the direct method and refined by the full-matrix least squares method in anisotropic-isotropic approximation on F^2. The hydrogen atoms were localized from the differential syntheses of electron density and refined by riding model. The final divergence factors wR_2 = 0.1677, GOF = 0.958 on reflections (R_1 = 0.0605 was

calculated on 4752 reflections with $I > 2\sigma(I)$) were calculated using the SHELXTL PLUS program package.[23]

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