Structural Features of Titanium Complexes of Salicylaldiminato Derivatives of Amino Acids

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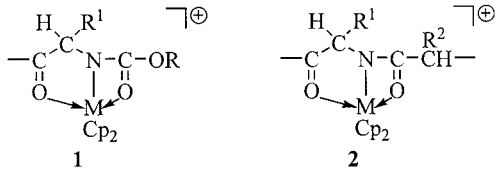
Condensation of salicylaldehyde with amino acid derivatives gave the salicylaldimine derivatives **3** that reacted with $TiCl_4$ with release of HCl to yield the chelate complexes [(SalPhgOMe)$TiCl_3$] (**4a**), [(SalValOMe)$TiCl_3$] (**4b**), and the dipeptide derivative [(SalAlaValOMe)$TiCl_3$] (**4d**). The complex [(Sal*PhgOMe)$TiCl_3$] (**4c**) was prepared analogously starting from 3,5-di-*tert*-butyl-2-hydroxybenzaldehyde and phenylglycine methyl ester. Complex *rac*-**4a** was characterized by X-ray diffraction and shown to feature a typical structure where the monoanionic ligand is tridentate, coordinating to the central titanium atom through both the phenolate oxygen atom and the ester carbonyl oxygen atom as well as through the imine nitrogen atom. A hydrolyzed carboxylate analogue of **4a** exhibits an analogous central structural framework. In this case, however, the overall structure of *rac*-**5a** was found to be a metallacyclic tetramer where four titanium atoms bind four such tridentate ligands.

Introduction

Group 4 metal complexes of peptide derivatives are receiving an increased interest lately. This section of the field of coordination chemistry[1] has become of increasing importance with regard to a variety of ongoing developments. Thus, titanium–protein complexes may play a role in the cancerostatic potential of some organometallic complexes of this light Group 4 element.[2,3] Titanium as well as zirconium complexes of modified peptide ligands have found some useful applications in enantioselective catalysis.[4,5] Heterogenized oligopeptide–zirconium complexes have been thought to exhibit an enzyme-like behavior in some organophosphate hydrolysis reactions,[6] to mention a few such recent developments and observations in this growing field.[7]

We had recently studied the chemistry and the structural features of the reaction products between [Cp_2TiMe^+] or [Cp_2ZrMe^+] cations with a variety of oligopeptide derivatives.[8,9] Addition and subsequent liberation of methane eventually resulted in a variety of stable products that all showed the structural motif of a tridentate chelate complex framework (see Scheme 1). In some cases a carbonyl group of a protective group (e.g. Boc) was involved (**1**), in other cases it was the C=O group of the next amino acid building block that made up one of the fused chelate ring systems (**2**).



Scheme 1.

It was the question whether we had here observed a special structural feature of a specific class of Group 4 metallocene–peptide complexes or if the observed structural motif in the systems **1/2** was an example of a general structural type in this area of coordination chemistry. For that reason we have investigated a number of remotely related titanium complexes derived from very electrophilic Group 4 metal components. We actually found favoured related structural frameworks in systems that were obtained from the reactions of $TiCl_4$ with salicylaldiminato derivatives of amino acids and dipeptides. Some representative examples are described and discussed in this article.

Results and Discussion

We have prepared a small series of salicylaldimine ligands (**3a**–**d**) by treatment of salicylaldehyde with the hydrochlorides of the respective amino acid methyl esters in dichloromethane with the aid of triethylamine.[10] For this study we have employed the amino acids (L)-phenylglycine and (L)-valine. For the synthesis of **3c** we have used 3,5-di-*tert*-butyl-2-hydroxybenzaldehyde as the coupling component. The chelate ligand **3d** was prepared by condensation

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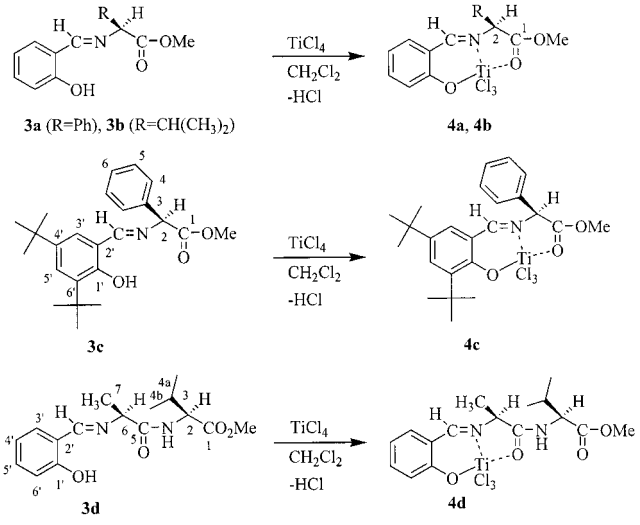
of salicylaldehyde with the peptide derivative HAlaValOMe (employed as the TFA adduct).

Treatment of the ligand system **3a** with $TiCl_4$ proceeded cleanly in dichloromethane solution with cleavage of HCl (Scheme 2). After a reaction time of ca. 1.5 h, the complex formation was complete. After workup, the product **4a** was isolated as a red solid in ca. 90% yield. The corresponding titanium complexes [(SalValOMe)$TiCl_3$] (**4b**), [(Sal*PhgOMe)$TiCl_3$] (**4c**), and the dipeptide-derived product [(SalAlaValOMe)$TiCl_3$] (**4d**) were synthesized analogously by treatment of the free HO-containing ligands with $TiCl_4$ in dichloromethane with cleavage of 1 equiv. of HCl. The reactions were practically quantitative, and these products were isolated in yields between 85% and 96%.



Scheme 2.

The complexes **4a**–**d** were characterized spectroscopically (see below) and by C,H,N elemental analyses. Single crystals of **4a** were obtained from a saturated THF solution at –22 °C, which allowed characterization by an X-ray crystal structure analysis (see Figure 1). The (SalPhgOMe) system is sensitive to racemization, and it seems that the racemate of the corresponding Ti complex (*rac*-**4a**) crystallizes much easier than its pure enantiomers. Therefore, we have only obtained single crystals of *rac*-**4a** (and consequently also of its derivative *rac*-**5a**) for the X-ray crystal structure analyses, despite numerous attempts to crystallize the enantiomerically pure compounds. Therefore, the degree of enantiomeric purity of the complexes **4**, derived from single amino acids, must remain open at this time. In the case of the dipeptide derivative **4d**, we only observed a single diastereoisomer by NMR spectroscopy, which indicates that enantiomerization at the proximal amino acid (Ala) in this (and probably the related **4b**) system, seems not to be a serious problem under the applied conditions. The ligands **3a** (SalPheOMe) and **3b** (SalValOMe) crystallized as the pure enantiomers (for details see the Exp. Sect. and the Supporting Information; for Supporting Information see also the footnote on the first page of this article).

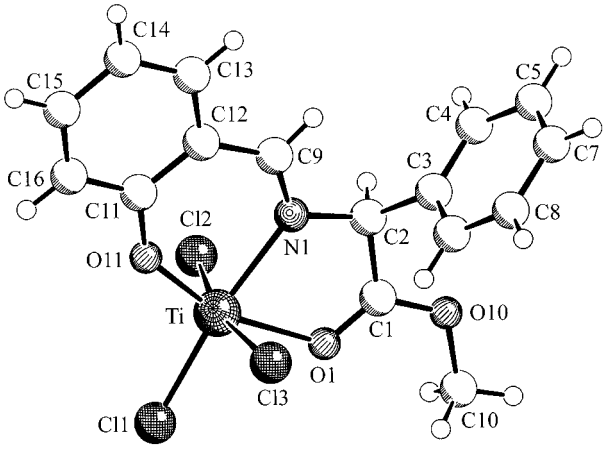


Figure 1. View of the molecular structure of the [(SalPhgOMe)-$TiCl_3$] complex *rac*-**4a**; selected bond lengths [Å] and angles [°]: Ti–Cl1 2.265(1), Ti–Cl2 2.327(1), Ti–Cl3 2.319(1), Ti–N1 2.177(2), Ti–O1 2.111(2), Ti–O11 1.797(2), C1–O10 1.303(3), C1–C2 1.507(3), C2–C3 1.520(3), C2–N1 1.482(3), N1–C9 1.281(3), C9–C12 1.448(3), C11–O11 1.346(3); Cl1–Ti–Cl2 93.9(1), Cl1–Ti–Cl3 94.7(1), Cl1–Ti–N1 171.3(1), Cl1–Ti–O1 96.5(1), Cl1–Ti–O11 104.1(1), Cl2–Ti–Cl3 165.3(1), Cl2–Ti–N1 84.6(1), Cl2–Ti–O1 83.9(1), Cl2–Ti–O11 95.3(1), Cl3–Ti–N1 85.1(1), Cl3–Ti–O1 83.3(1), Cl3–Ti–O11 94.2(1), N1–Ti–O1 74.9(1), N1–Ti–O11 84.5(1), O1–Ti–O11 159.4(1), Ti–O1–C1 119.8(1), O1–C1–O10 123.5(2), O1–C1–C2 121.9(2), O10–C1–C2 114.5(2), C1–C2–N1 106.2(2), C2–N1–C9 118.0(2), Ti–N1–C2 116.1(1), Ti–N1–C9 125.9(1), Ti–O11–C11 141.0(1). For additional values see the text.

In complex *rac*-**4a** the (SalPhgOMe) ligand binds to the titanium atom through the phenolic oxygen atom, the imine nitrogen atom and the ester carbonyl oxygen atom. The core atoms of this tridentate chelate ligands are oriented close to planar. The bond between Ti and the phenolic oxygen atom O11 is short [1.797(2) Å] and the corresponding Ti–O11–C11 angle [141.0(1)°] is substantially enlarged.[11] The Ti–N1 linkage amounts to 2.177(2) Å, with the C9–N1 bond [1.281(3) Å] being in the typical C=N double bond range.[12] The nitrogen atom N1 shows a trigonal-planar coordination geometry [Ti–N1–C9: 125.9(1)°, Ti–N1–C2: 116.1(1)°, C9–N1–C2: 118.0(2)°]. The Ti–O1 distance is 2.111(2) Å, and the corresponding C1–O1–Ti angle was found at 119.8(1)°. The C1–O1 length [1.229(3) Å] is in the typical carbonyl C=O double bond range. The adjacent C1–O10 bond is much longer at 1.303(3) Å.

The coordination geometry at the central titanium atom is distorted octahedral. There is a pronounced *trans* effect: The Ti–Cl1 bond (*trans* to N1) is much shorter [2.265(1) Å] than the Ti–Cl2 [2.327(1) Å] and Ti–Cl3 [2.319(1) Å] bonds. The three *trans* angles amount to 171.3(1)° (Cl1–Ti–N1), 165.3(1)° (Cl2–Ti–Cl3) and 159.4(1)° (O1–Ti–O11). Ten of the twelve *cis* angles are within a narrow range between 83.3(1)° and 96.5(1)°. Only the N1–Ti–O1 angle is markedly smaller at 74.9(1)°, which probably is a typical feature of the five-membered chelate substructure. Consequently, the adjacent O11–Ti–Cl1 angle is widened to 104.1(1)°.

Complex **4a** seems to adopt a similar structure in solution. The ^{13}C NMR spectra clearly indicate the coordina-

tion of the ester carbonyl group. On going from the ligand (**3a**: δC1 = 171.1 ppm) to the complex **4a** (δC1 = 182.3 ppm) this carbonyl carbon resonance is shifted to larger δ values by $\Delta\delta$ = +11.2 ppm. This is very characteristic for the formation of a Ti–O=C metal coordination.[8,9] The coordination is also evidenced by a similar shifting of the adjacent OCH_3 resonances on going from **3a** to **4a** (^{1}H: $\Delta\delta$ = +0.48 ppm; ^{13}C: $\Delta\delta$ = +6.8 ppm; see Table 1). The evidence for the imine coordination to the titanium atom comes from a comparison of the ^{15}N NMR spectra. Complex **4a** features a ^{15}N NMR imine nitrogen resonance at δ = –104.9 ppm, which is shifted by $\Delta\delta$ = –16.3 ppm relative to the noncoordinated **3a** reference. In contrast, the increased coordination number of the imine nitrogen atom in **4a** does not lead to very characteristic differences in the ^{13}C ($\Delta\delta$ = –1.9 ppm) or ^{1}H NMR spectra. The complexes **4b**–**d** show similar spectroscopic features (see Table 1), so that we must assume analogous solution structures of these compounds featuring tridentate salicylaldimine/amino acid derived chelate ligands.

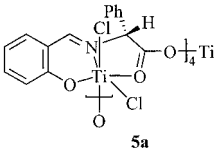
Table 1. Comparison of selected ^{1}H and ^{13}C NMR spectroscopic data of the ligand systems **3** and their corresponding metal complexes **4** .[a]

	3a	**4a**	**3b**	**4b**	**3c**	**4c**	**3d**	**4d**
C*H*=N	8.40	7.99	8.33	8.35	8.42	8.00	8.44	8.46
*C*H=N	167.1	165.2	167.5	164.2	168.6	166.3	167.4	164.0
N*C*H	75.1	75.6	78.5	78.0	75.0	75.6	68.8	69.2
NC*H*	5.20	5.99	3.77	4.62	5.20	5.97	4.05	5.26
C=O	171.1	182.3	172.2	183.5	171.3	182.4	172.0	179.2
O*C*H$_3$	52.0	58.8	52.7	58.4	52.9	58.8	172.4[b]	171.1[b]
OC*H*$_3$	3.75	4.23	3.74	4.32	3.76	4.24	3.69[c]	3.84[c]

[a] ^{1}H/^{13}C NMR spectra in CD_2Cl_2. [b] Terminal –CO_2CH_3 carbonyl group. [c] Terminal –OCH_3 group.

During an attempt to crystallize complex **4a** from dichloromethane, apparently some of the compound was unintendedly hydrolyzed and single crystals of the Ti–chelate carboxylate complex *rac*-**5a** were isolated (see Scheme 3). In the crystal state this complex attains an interesting tetranuclear structure (see Figures 2 and 3) in which the chelate carboxylates have become connected in a metallacyclic fashion by means of a bridging octahedrally coordinated quartet of titanium atoms. The coordination of each of the four subunits is chemically equivalent, although crystallographically slightly different. Again, we find the same structural framework motif that was already observed in the related monomeric complex **4a** (see above). This shall be illustrated with the subunit A in the tetramer of **5a** in the crystal.

The substructures of *rac*-**5a** feature the typical array of Ti–O/N bonds at their distorted octahedral Ti atom. In the subunit A of *rac*-**5a** the Ti–O3 bond length is 1.803(4) Å, which is almost as short as the respective bond in *rac*-**4a** (see above). The Ti–N1 linkage in *rac*-**5a** amounts to 2.164(5) Å, the adjacent C3–N1 double bond has a length of 1.274(7) Å. The O1–Ti distance in *rac*-**5a** was found at 2.002(4) Å, and the C1–O1 bond [1.267(6) Å] is in the typical carboxylate C=O bond range.[12] The C1–O2 distance in the Ti–carboxylate is in a similar range [1.247(6) Å]. The O2(A)–Ti1(B) bond length amounts to 2.054(4) Å. The Ti1(A)–O2(D) distance is 2.086(4) Å. Together with the pair of remaining chloride ligands [Ti–Cl1: 2.262(2) Å; Ti–Cl2: 2.261(2) Å] this completes the distorted octahedral co-



Scheme 3.

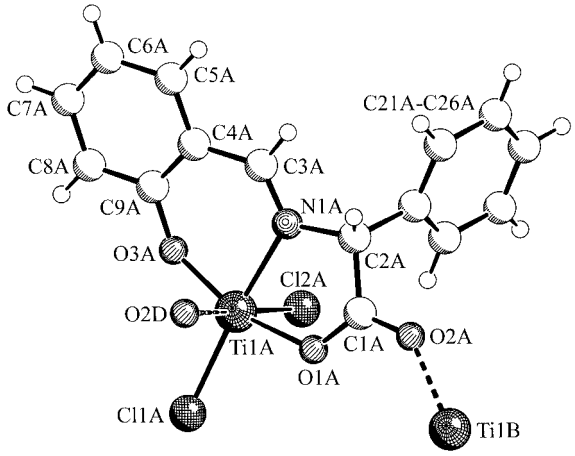


Figure 2. Projection of a typical mononuclear chelate complex subunit of the cyclotetramer *rac*-**5a**.

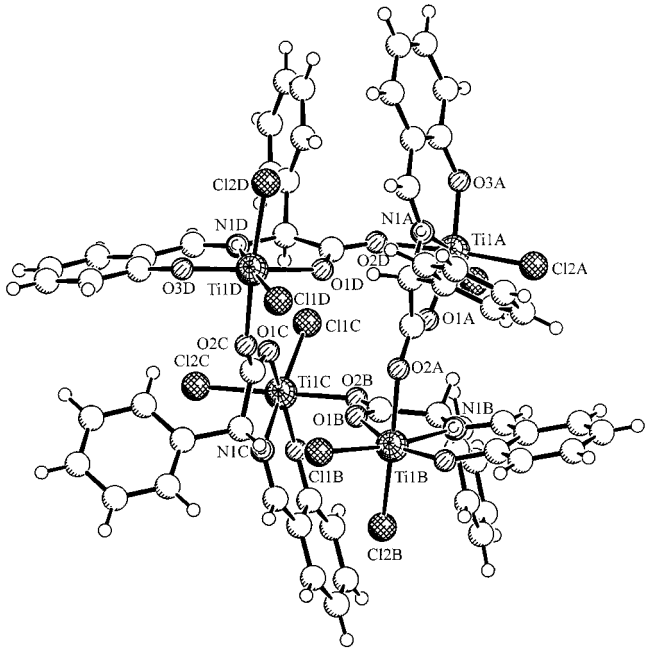
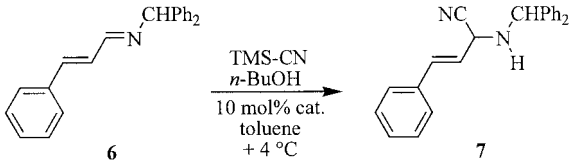


Figure 3. View of the tetrameric cyclic structure of complex *rac*-**5a**.

ordination geometry around the central titanium atom of this subunit. As expected, the three *trans* angles deviate in a typical manner from the ideal 180° [O3A–Ti1A–O1A: 157.3(2)°; O2D–Ti1A–Cl2A: 173.7(1)°; N1A–Ti1A–Cl1A: 169.4(1)°]. The *cis* angles are in a narrow range between 83.6(2)° and 97.6(2)°, again with the exception of the small O1A–Ti1A–N1A angle inside the five-membered ring substructure of the chelate [75.0(2)°]. As previously observed for the structure of *rac*-**4a**, this also leads to an increased O3A–Ti1A–Cl1A angle [104.2(2)°] in the Ti–carboxylate *rac*-**5a**.

The complexes **4** were briefly checked for their catalytic activity. For this characterization we used the hydrocyanation reaction of **6** to yield **7** (see Scheme 4), a system that was described previously by Hoveyda et al.[5,13] The complexes **4b**–**d** were employed. They all were more active than the in situ catalyst, generated by treatment of **3b** with $Ti(OiPr)_4$. Not unexpectedly, we did not observe any asymmetric induction with any of these simple catalyst systems under the applied reaction conditions at +4 °C.[4,5] However, the conversion of **6** to **7** showed very low *ee* values of ca. 6–9%, when carried out with the **4b** catalyst system at –78 °C.



Scheme 4.

Conclusions

This study has shown that $TiCl_4$ reacts with the salicylaldimine derivatives **3** with cleavage of HCl to give tridentate chelate complex structures of a type which is reminiscent of the oligopeptide–metallocene cation complexes that we had obtained and structurally characterized previously (see Scheme 1).[8,9] It seems that the electrophilic Group 4 metals in general favour the formation of such tridentate chelate structures whenever it is possible. In the case of the peptide-derived systems **1** and **2** (see above) tridentate chelate complex frameworks were formed, featuring anellated five- and four-membered ring structures, whereas in the case of the systems **4** the salicylaldimine moiety was involved in the formation of a closely related framework built up of anellated six- and five-membered chelate ring systems. Since these chelate structures form so easily, it can probably be assumed that similar structures are also readily available in the reactions of such ligand precursors with e.g. $Ti(OiPr)_4$. It may be that such structures play an important role in the respective catalyst systems, as proposed,[5] although in the previous studies the catalysts were usually generated in situ and not isolated or structurally characterized. Since the isolated complexes **4** are catalytically active, it may be tempting to actually prepare, isolate and structurally characterize such a catalyst by using an optimized longer oligopeptide-derived ligand system known from the literature[5] to gain direct experimental evidence of the stereochemical features of such active catalyst systems.

Experimental Section

General Remarks: Reactions with air- and moisture-sensitive compounds or reagents were carried out under argon using Schlenk-type glassware or in a glovebox. Solvents were dried and distilled under argon prior to use. For additional general information, including a list of the instruments used for physical characterization of the compounds see refs.[8,9] For the atom numbering scheme used in the NMR listings, see Scheme 2. Most NMR assignments were secured by additional 2D NMR experiments [^1H-^{15}N ghmbc experiment based on an $^nJ(^{15}N,^1H)$ coupling constant of 5 Hz].[14]

X-ray Crystal Structure Analyses: Data sets were collected with Enraf Nonius CAD4 and Nonius KappaCCD diffractometers, in case of Mo radiation, equipped with a rotating anode generator. Programs used: Data collection EXPRESS (Nonius B.V., **1994**) and COLLECT (Nonius B.V., **1998**), data reduction MolEN (K. Fair, Enraf–Nonius B. V., **1990**) and Denzo-SMN (Z. Otwinowski, W. Minor, *Methods in Enzymology*, **1997**, *276*, 307–326), absorption correction for CCD data SORTAV (R. H. Blessing, *Acta Crystallogr.* **1995**, *A51*, 33–37; R.H. Blessing, *J. Appl. Crystallogr.* **1997**, *30*, 421–426) and Denzo (Z. Otwinowski, D. Borek, W. Majewski, W. Minor, *Acta Crystallogr.* **2003**, *A59*, 228–234), structure solution SHELXS-97 (G. M. Sheldrick, *Acta Crystallogr.* **1990**, *A46*, 467–473), structure refinement SHELXL-97 (G. M. Sheldrick, University of Göttingen, **1997**), graphics SCHAKAL (E. Keller, **1997**) and DIAMOND (K. Brandenburg, University of Bonn, **1997**). CCDC-261081, -261082, -261560 and -261561 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Preparation of the Salicylaldimines

SalPhgOMe (3a): Triethylamine (2.48 g, 24.6 mmol, 1.05 equiv.) was added to a suspension of HCl·H–Phg–OMe (3.00 g, 24.6 mmol, 1.05 equiv.) in dichloromethane (40 mL). After addition of salicylaldehyde (4.71 g, 23.4 mmol, 1.00 equiv.), the colour of the solution turned yellow and the reaction mixture was stirred at room temperature overnight. The solution was washed twice with water and the organic layer dried with magnesium sulfate. Removal of the solvent (at ca. +5 °C to avoid racemisation) led to a yellow solid (5.36 g, 19.9 mmol, 85%). Single crystals for the X-ray crystal structure analysis were obtained by crystallisation from ethanol at –22 °C. M.p. 65.6 °C. $C_{16}H_{15}NO_3$ (269.3): calcd. C 71.63, H 5.61, N 5.20; found C 71.33, H 5.63, N 5.22. $[\alpha]_D^{20} = -26.8$ ($c = 0.3$, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 2949, 2743, 2675, 2492, 1749, 1629, 1576, 1496, 1464, 1440, 1405, 1315, 1281, 1258, 1209, 1167, 1150, 1127, 1092, 1060, 1036, 982, 854, 776, 758, 742, 731, 697, 612, 561, 521 cm^{-1}. ^1H NMR (300.1 MHz, CD_2Cl_2, 298 K): δ = 13.06 (s, 1 H, OH), 8.40 (s, 1 H, CH=N), 7.46–7.26 (m, 7 H, H_{phenyl}), 6.98–6.89 (m, 2 H, H_{phenyl}), 5.20 (s, 1 H, 2-H), 3.75 (s, 3 H, OCH_3) ppm. $^{13}C\{^1H\}$ NMR (75.5 MHz, CD_2Cl_2, 298 K): δ = 171.1 (C-1), 167.4 (CH=N), 161.4 (C–OH), 137.7, 133.3, 132.4, 129.3, 128.8, 128.2, 119.6, 117.3 (C_{phenyl}), 75.1 (C-2), 53.0 (OCH_3) ppm. GHMBC (60.8/599.8 MHz, CD_2Cl_2, 298 K): δ (^{15}N)/δ(^1H) = –88.6/13.06, 8.40, 5.20 (CH=*N*/1′-O*H*, C*H*=N, 2-H) ppm.

SalValOMe (3b): According to the preparation of **3a**, HCl·H–ValOMe (3.00 g, 17.9 mmol) was treated with triethylamine (1.81 g,

17.9 mmol) and salicylaldehyde (2.08 g, 17.0 mmol) to yield **3b** as a yellow solid (3.32 g, 14.1 mmol, 83%). Single crystals for the X-ray crystal structure analysis were obtained by crystallisation from a 1:1 mixture of pentane/diethyl ether at –22 °C. M.p. 34.9 °C. $C_{13}H_{17}NO_3$ (235.3): calcd. C 66.36, H 7.28, N 5.95; found C 66.37, H 7.26, N 5.85. $[\alpha]_D^{20}$ = –38.4 (*c* = 1.0, $CHCl_3$), IR (KBr): $\tilde{\nu}$ = 2955, 2344, 1736, 1625, 1573, 1493, 1455, 1429, 1409, 1338, 1368, 1331, 1305, 1276, 1196, 1173, 1137, 1115, 1060, 1032, 1020, 977, 880, 847, 762, 736, 675, 663, 601, 549, 461 cm^{-1}. ^1H NMR (300.1 MHz, CD_2Cl_2, 298 K): δ = 13.11 (s, 1 H, OH), 8.33 (s, 1 H, CH=N), 7.40–7.30 (m, 2 H, H_{phenyl}), 6.97–6.85 (m, 2 H, H_{phenyl}), 3.77 (d, ^3J = 6.3 Hz, 1 H, 2-H), 3.74 (s, 3 H, OCH_3), 2.38 (m, 1 H, CH_{iPr}), 0.97 (d, ^3J = 6.8 Hz, 6 H, 2 CH_3) ppm. $^{13}C\{^1H\}$ NMR (75.5 MHz, CD_2Cl_2, 298 K): δ = 172.2 (C-1), 167.5 (CH=N), 162.0 (C–OH), 133.5, 132.5, 119.4, 117.7 (C_{phenyl}), 78.5 (C-2), 52.7 (OCH_3), 32.7 (CH_{iPr}), 19.9, 18.7 (2 CH_3) ppm.

Sal*PhgOMe (3c): Triethylamine (173 mg, 1.70 mmol, 1.00 equiv.) was added to a solution of HCl·H–Phg–OMe (344 mg, 1.70 mmol, 1.00 equiv.) in ethanol (20 mL). After addition of 3,5-di-*tert*-butyl-2-hydroxybenzaldehyde (400 mg, 1.70 mmol, 1.00 equiv.), the reaction mixture was stirred at room temperature for 3 d. The solvent was removed and the residue taken up in dichloromethane (20 mL). The yellow solution was washed twice with an aqueous 5% $NaHCO_3$ solution (20 mL) and once with water (20 mL). The organic layer was dried with magnesium sulfate and removal of the solvent led to 532 mg (1.39 mmol, 82%) of a yellow solid. M.p. 93.0 °C. $C_{24}H_{31}NO_3$ (381.5): calcd. C 75.56, H 8.19, N 3.67; found C 75.43, H 8.27, N 3.44. $[\alpha]_D^{20}$ = –6.9 (*c* = 0.16, CH_2Cl_2). IR (KBr): $\tilde{\nu}$ = 3482, 3417, 2961, 2869, 1752, 1630, 1474, 1452, 1439, 1391, 1365, 1322, 1274, 1252, 1200, 1161, 1087, 1065, 835, 726, 696, 504 cm^{-1}. ^1H NMR (599.8 MHz, CD_2Cl_2, 298 K): δ = 13.49 (s, 1 H, OH), 8.42 (s, 1 H, CH=N), 7.48 (m, 2 H, 4-H), 7.43 (AB, ^4J = 2.4 Hz, 1 H, 5′-H), 7.41 (m, 2 H, 5-H), 7.36 (m, 1 H, 6-H), 7.12 (AB, ^4J = 2.4 Hz, 1 H, 3′-H), 5.20 (s, 1 H, 2-H), 3.76 (s, 3 H, OCH_3), 1.46 [s, 9 H, 6′–$C(CH_3)_3$], 1.30 [s, 9 H, 4′-$C(CH_3)_3$] ppm. $^{13}C\{^1H\}$ NMR (150.8 MHz, CD_2Cl_2, 298 K): δ = 171.3 (C-1), 168.6 (CH=N), 158.3 (C-1′), 140.9 (C-4′), 137.9 (C-3), 137.1 (C-6′), 129.3 (C-5), 128.8 (C-6), 128.2 (C-4), 128.2 (C-5′), 127.0 (C-3′), 118.2 (C-2′), 75.0 (C-2), 52.9 (OCH_3), 35.3 [6′-*C*(CH_3)$_3$], 34.4 [4′-*C*(CH_3)$_3$], 31.5 [4′-C(*C*H$_3$)$_3$], 29.5 [6′-C(*C*H$_3$)$_3$] ppm.

SalAlaValOMe (3d): Triethylamine (320 mg, 3.16 mmol, 1.05 equiv.) was added to a solution of TFA·H–Ala–Val–OMe (1.00 mg, 3.16 mmol, 1.05 equiv.) in ethanol (20 mL). After addition of salicylaldehyde (367 mg, 3.01 mmol, 1.00 equiv.), the reaction mixture was stirred at room temperature for 2 d. The solvent was removed and the residue taken up in dichloromethane (20 mL). The yellow solution was washed twice with an aqueous 5% $NaHCO_3$ solution (20 mL) and once with water (20 mL). The organic layer was dried with magnesium sulfate and removal of the solvent led to 692 mg (2.26 mmol, 75%) of a yellow oil. $C_{16}H_{22}N_2O_4$ (306.4): calcd. C 62.73, H 7.24, N 9.14; found C 62.72, H 7.05, N 9.05. $[\alpha]_D^{20}$ = +112.0 (*c* = 0.1, CH_2Cl_2). IR (KBr): $\tilde{\nu}$ = 3426, 2965, 2926, 2869, 2365, 1739, 1669, 1626, 1587, 1517, 1465, 1435, 1369, 1317, 1283, 1204, 1152, 1034, 912, 756, 626 cm^{-1}. ^1H NMR (499.8 MHz, C_6D_6, 298 K): δ = 12.85 (s, 1 H, OH), 7.53 (s, 1H CH=N), 7.02 (m, 1 H, 6′-H), 7.00 (m, 1 H, 4′-H), 6.80 (ABCD, ^3J = 7.7, ^4J = 1.4 Hz, 1 H, 3′-H), 6.64 (ABCD, ^3J = 7.5, ^4J = 1.6 Hz, 1 H, 5′-H), 6.61 (d, ^3J = 8.7 Hz, 1 H, NH), 4.77 (m, 1 H, 2-H), 3.64 (q, ^3J = 6.8 Hz, 1 H, 6-H), 3.17 (s, 3 H, OCH_3), 2.03 (m, 1 H, 3-H), 1.34 (d, ^3J = 6.9 Hz, 3 H, 7-H), 0.85 (d, ^3J = 6.9 Hz, 3 H, 4a-H), 0.77 (d, ^3J = 6.9 Hz, 3-H, 4b-H) ppm. $^{13}C\{^1H\}$ NMR (125.7 MHz, C_6D_6, 298 K): δ = 172.0 (C-1), 171.5 (C-5), 167.1 (CH=N), 161.6 (C-1′), 133.2 (C-4′), 132.3 (C-3′), 119.0 (C-5′), 118.9 (C-2′), 117.5 (C-6′), 68.6 (C-6), 57.1 (C-2), 51.5 (OCH_3), 31.4 (C-3), 20.9 (C-7), 19.0 (C-4a), 17.5 (C-4b) ppm.

Preparation of the Titanium Complexes

[(SalPhgOMe)TiCl$_3$] (4a): $TiCl_4$ (1.10 g, 5.79 mmol, 1.00 equiv.) was added to a solution of SalPhgOMe (**3a**) (1.56 g, 5.79 mmol, 1.00 equiv.) in dichloromethane (20 mL). The colour of the solution immediately turned red. After stirring at room temperature for 1.5 h, the solvent was removed and the red solid (2.75 g, 5.21 mmol, 90%) dried in vacuo. Single crystals for the X-ray crystal structure analysis were obtained by crystallisation from THF at –22 °C. Decomp. 207.4 °C. $C_{16}H_{14}Cl_3NO_3Ti{\cdot}1.25CH_2Cl_2$ (528.7): calcd. C 39.19, H 3.15, N 2.65; found C 39.56, H 3.04, N 2.61. $[\alpha]_D^{20}$ = –43.2 (*c* = 0.25, CH_2Cl_2). IR (KBr): $\tilde{\nu}$ = 3439, 3062, 2960, 2870, 1649, 1616, 1596, 1560, 1496, 1475, 1453, 1370, 1273, 1251, 1228, 1156, 1123, 1051, 1030, 1005, 921, 841, 763, 734, 703, 661, 586, 551, 456, 427 cm^{-1}. ^1H NMR (499.8 MHz, CD_2Cl_2, 298 K): δ = 7.99 (d, ^4J = 2.0 Hz, 1 H, CH=N), 7.66 (ABCD, ^3J = 8.5, ^4J = 2.0 Hz, 1 H, 5′-H), 7.51 (m, 5 H, 4-H, 5-H u. 6-H), 7.39 (ABCD, ^3J = 8.5, ^4J = 1.5 Hz, 1 H, 3′-H), 7.19 (ABCD, ^3J = 8.5, ^4J = 1.0 Hz, 1 H, 4′-H), 6.91 (ABCD, ^3J = 8.5 Hz, 1 H, 6′-H), 5.99 (d, ^4J = 2 Hz, 1 H, 2-H), 4.23 (d, ^5J = 2 Hz, 3 H, OCH_3) ppm. $^{13}C\{^1H\}$ NMR (125.7 MHz, CD_2Cl_2, 298 K): δ = 182.3 (C-1), 165.2 (CH=N), 162.1 (C-1′), 137.8 (C-5′), 135.7 (C-3′), 133.6 (C-3), 130.8 (C-5), 130.4 (C-4 u. C-6), 125.8 (C-2′), 125.6 (C-4′), 114.9 (C-6′), 75.6 (C-2), 58.8 (OCH_3). GHMBC (60.8/599.8 MHz, CD_2Cl_2, 298 K): δ (^{15}N)/δ (^1H) = –104.9/7.99 (CH=*N*/C*H*=N) ppm.

X-ray Crystal Structure Analysis of *rac*-4a: Formula $C_{16}H_{14}Cl_3NO_3Ti{\cdot}3C_4H_8O$, *M* = 638.84, red crystal 0.35 × 0.20 × 0.15 mm, *a* = 10.396(1), *b* = 19.708(1), *c* = 15.139(1) Å, β = 91.83(1)°, *V* = 3100.2(4) $Å^3$, $\rho_{calcd.}$ = 1.369 g cm^{-3}, μ = 5.75 cm^{-1}, empirical absorption correction (0.824 ≤ *T* ≤ 0.919), *Z* = 4, monoclinic, space group $P2_1/c$ (No. 14), λ = 0.71073 Å, *T* = 198 K, ω- and φ-scans, 20865 reflections collected (±*h*, ±*k*, ±*l*), [(sinθ)/λ] = 0.66 $Å^{-1}$, 7378 independent (R_{int} = 0.037) and 5630 observed reflections [$I \geq 2\sigma(I)$], 353 refined parameters, *R* = 0.048, wR_2 = 0.121, max./min. residual electron density 0.46/–0.47 e·$Å^{-3}$, hydrogen atoms calculated and refined as riding atoms.

[(SalValOMe)TiCl$_3$] (4b): According to the preparation of **4a**, SalValOMe (**3b**) (500 mg, 2.13 mmol) was treated with $TiCl_4$ (403 mg, 2.13 mmol) to yield **4b** as a red solid (850 mg, 2.04 mmol, 96%). Decomp. 207.4 °C. $C_{13}H_{16}Cl_3NO_3Ti{\cdot}1/3CH_2Cl_2$ (416.8): calcd. C 38.42, H 4.03, N 3.36; found C 38.48, H 3.93, N 3.50. $[\alpha]_D^{20}$ = +204.4 (*c* = 0.125, CH_2Cl_2). IR (KBr): $\tilde{\nu}$ = 2966, 2934, 2874, 1752, 1643, 1598, 1460, 1399, 1377, 1318, 1273, 1251, 1227, 1155, 1123, 1098, 1055, 984, 920, 844, 759, 663, 558, 456, 416 cm^{-1}. ^1H NMR (599.8 MHz, CD_2Cl_2, 298 K): δ = 8.35 (s, 1 H, CH=N), 7.69 (ABCD, ^3J = 7.8, ^4J = 1.5 Hz, 1 H, 5′-H), 7.63 (ABCD, ^3J = 7.8, ^4J = 1.5 Hz, 1 H, 3′-H), 7.25 (ABCD, ^3J = 7.8, ^4J = 1.2 Hz, 1 H, 4′-H), 6.89 (ABCD, ^3J = 7.8 Hz, 1 H, 6′-H), 4.62 (dd, ^3J = 5.9, ^4J = 0.8 Hz, 1 H, 2-H), 4.32 (s, 3H OCH_3), 2.64 (m, 1 H, 3-H), 1.20 (d, ^3J = 6.8 Hz, 3 H, 4a-H), 1.16 (d, ^3J = 6.8 Hz, 3 H, 4b-H) ppm. $^{13}C\{^1H\}$ NMR (150.8 MHz, CD_2Cl_2, 298 K): δ = 183.5 (C-1), 164.2 (CH=N), 162.0 (C-1′), 137.7 (C-5′), 135.8 (C-3′), 125.8 (C-2′), 125.5 (C-4′), 114.9 (C-6′), 78.0 (C-2), 58.4 (OCH_3), 34.7 (C-3), 20.7 (C-4a), 19.0 (C-4b) ppm.

[(Sal*PhgOMe)TiCl$_3$] (4c): According to the preparation of **4a**, Sal*PhgOMe (**3c**) (200 mg, 0.52 mmol) was treated with $TiCl_4$ (100 mg, 0.52 mmol) to yield **4c** as a red solid (330 mg, 0.44 mmol, 85%). Decomp. 336.5 °C. $C_{24}H_{30}Cl_3NO_3Ti{\cdot}2.5CH_2Cl_2$ (747.1): calcd. C 42.60, H 4.72, N 1.87; found C 42.95, H 4.58, N 2.18. $[\alpha]_D^{20}$ = –27.3 (*c* = 0.08, CH_2Cl_2). IR (KBr): $\tilde{\nu}$ = 3065, 2961, 2907, 2869, 1654, 1613, 1565, 1553, 1454, 1400, 1365, 1325, 1268, 1249,

1211, 1185, 1051, 1030, 1010, 922, 873, 822, 764, 728, 699, 614, 603, 584, 541, 456 cm^{-1}. ^1H NMR (599.8 MHz, CD_2Cl_2, 298 K): δ = 8.00 (d, ^4J = 1.5 Hz, 1 H, CH=N), 7.72 (d, ^4J = 2.2 Hz, 1 H, 5′-H), 7.52 (m, 5 H, 4-H, 5-H, 6-H), 7.22 (d, ^3J = 2.3 Hz, 1 H, 3′-H), 5.97 (s, 1 H, 2-H), 4.24 (s, 3 H, OCH_3), 1.55 [s, 9 H, 6′-C$(CH_3)_3$], 1.28 [s, 9 H, 4′-C$(CH_3)_3$] ppm. $^{13}C\{^1H\}$ NMR (150.8 MHz, CD_2Cl_2, 298 K): δ = 182.4 (C-1), 166.3 (CH=N), 159.8 (C-1′), 148.7 (C-4′), 136.8 (C-6′), 133.8 (C-3), 133.1 (C-5′), 130.9 (C-3′), 130.8 (C-6), 130.4 (C-5), 130.3 (C-4), 126.7 (C-2′), 75.6 (C-2), 58.8 (OCH_3), 35.8 [6′-*C*$(CH_3)_3$], 35.1 [4′-*C*$(CH_3)_3$], 31.2 [4′-C(*C*$H_3)_3$], 29.9 [6′-C(*C*$H_3)_3$] ppm.

[(SalAlaValOMe)TiCl$_3$] (4d): According to the preparation of **4a**, SalAlaValOMe (**3d**) (250 mg, 0.82 mmol) was treated with $TiCl_4$ (155 mg, 0.82 mmol) to yield **4d** as a red solid (830 mg, 0.75 mmol, 92%). Decomp. 118.2 °C. $C_{16}H_{21}Cl_3N_2O_4Ti{\cdot}7.5CH_2Cl_2$ (1096.6): calcd. C 25.74, H 3.31, N 2.55; found C 25.36, H 2.92, N 3.32. $[\alpha]_D^{20}$ = +60.6 (*c* = 0.18, CH_2Cl_2). IR (KBr): $\tilde{\nu}$ = 3282, 2965, 1743, 1622, 1600, 1556, 1448, 1396, 1274, 1248, 1226, 1143, 930, 826, 756, 657, 552, 426 cm^{-1}. ^1H NMR (499.8 MHz, CD_2Cl_2, 298 K): δ = 8.46 (s, 1 H, CH=N), 7.84 (d, ^3J = 8.3 Hz, 1 H, 2-NH), 7.64 (m, 2 H, 3′-H u. 5′-H), 7.22 (ABCD, ^3J = 7.6, ^4J = 1.0 Hz, 1 H, 4′-H), 6.87 (ABCD, ^3J = 8.6 Hz, 1 H, 6′-H), 5.26 (q, ^3J = 7.2 Hz, 1 H, 6-H), 4.75 (dd, ^3J = 8.6 Hz, 1 H, 2-H), 3.84 (s, 3 H, OCH_3), 2.24 (m, 1 H, 3-H), 1.87 (d, ^3J = 7.5 Hz, 3 H, 7-H), 0.97 (d, ^3J = 6.7 Hz, 3 H, 4a-H), 0.88 (d, ^3J = 6.7 Hz, 3 H, 4b-H) ppm. $^{13}C\{^1H\}$ NMR (125.7 MHz, CD_2Cl_2, 298 K): δ = 179.2 (C-5), 171.1 (C-1), 164.0 (CH=N), 161.7 (C-1′), 137.4 (C-5′), 135.4 (C-3′), 125.6 (C-2′), 125.1 (C-4′), 115.0 (C-6′), 69.2 (C-6), 60.3 (C-2), 53.5 (OCH_3), 31.8 (C-3), 22.8 (C-7), 19.2 (C-4a), 17.8 (C-4b) ppm.

X-ray Crystal Structure Analysis of *rac*-5a: Formula $C_{15}H_{11}Cl_2NO_3Ti{\cdot}CH_2Cl_2$, M = 456.97, red crystal 0.25 × 0.10 × 0.07 mm, a = 14.182(1), b = 14.401(1), c = 19.735(1) Å, α = 75.70(1), β = 89.91(1), γ = 85.97(1)°, V = 3895.5(4) Å^3, $\rho_{calcd.}$ = 1.558 g cm^{-3}, μ = 10.02 cm^{-1}, empirical absorption correction (0.788 ≤ T ≤ 0.933), Z = 8, triclinic, space group $P\bar{1}$ (No. 2), λ = 0.71073 Å, T = 198 K, ω- and φ-scans, 37081 reflections collected (±h, ±k, ±l), [(sinθ)/λ] = 0.62 Å^{-1}, 15775 independent (R_{int} = 0.058) and 10717 observed reflections [$I \geq 2\ \sigma(I)$], 912 refined parameters, R = 0.080, wR_2 = 0.214, max./min. residual electron density 1.84/–0.97 e·Å^{-3} in the region of the solvent molecules, phenyl group C21B–C26B refined with split positions, some of the solvent molecules heavily disordered, refinement with split positions did not improve the model, hydrogen atoms calculated and refined as riding atoms.

Catalytic Hydrocyanation Reactions: The catalyst (0.043 mmol) was dissolved in toluene(2 mL) under argon. After stirring at room temperature for 10 min, imine **6** (0.43 mmol)[13] was added and the mixture was cooled to 4 °C. After an equilibration time of 20 min, trimethylsilyl cyanide (0.85 mmol) was added and a solution of *n*-butanol (0.64 mmol) in toluene (2 mL) was added through a syringe pump over a period of 10 h. After further stirring at 4 °C for 14 h, the reaction was quenched by the addition of diethyl ether (5 mL). Filtration through a plug of silica gel, removal of the solvent and crystallisation from a 1:1 mixture of diethyl ether/pentane at –22 °C yielded the product. Enantiomeric analysis was carried out by HPLC (Kromasil, KR100-5CHI-TBB, 250 × 4.6 mm, flow 0.5 mL/min, *n*-hexane) after a reaction time of 12 and 24 h, respectively. Details are provided with the Supporting Information.

Supporting Information (see also footnote on the first page of this article): Additional spectroscopic data of the compounds **3** and **4**; X-ray crystal structure analyses of the compounds **3a** and **3b**; details of the catalytic hydrocyanation reactions.

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