Reaction of "Jordan's Cation" $[Cp_2ZrCH_3(thf)]^+$ with Amino Acid-Derived Isocyanates—A First Synthetic Route to Oligopeptide-Modified Group 4 Bent Metallocene Cation Systems

Markus Oberhoff, Gerhard Erker,* and Roland Fröhlich

Dedicated to Professor Waldemar Adam on the occasion of his 65th birthday

Abstract: The organometallic cation $[Cp_2ZrCH_3(thf)]^+$, employed as the tetraphenylborate salt (**1**), reacts cleanly in 1:1 stoichiometry with the isocyanates **2** derived from valine methyl ester or valylvaline methyl ester, respectively. In each case addition of the $Zr-CH_3$ group to the isocyanate sp-carbon center is observed with formation of a functionalized zirconocene cation derivative containing a chelating *N*-metallated *N*-acetylvaline methyl ester (**3a**) or *N*-acetylvalylvaline methyl ester (**3b**) moiety, respectively, coordinated in the bent metallocene σ-ligand plane. The spectroscopic data of **3**, supported by an X-ray crystal structure analysis of the zirconated dipeptide derivative **3b**, have revealed the presence of chelating (η^1-O:η^1-N)-coordination of the terminal *N*-acetyl groups in addition to a Zr–O=C interaction with the adjacent valyl amido group.

Keywords
isocyanates · "Jordan's cation" · metallocenes · peptides · zirconium

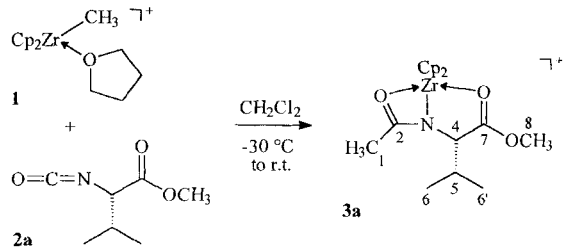
Introduction

"Jordan's cation", $[Cp_2ZrCH_3(thf)]^+$, is used extensively as a reagent in organometallic chemistry and catalysis. Its advent initiated pioneering studies towards a profound understanding of the essential mechanistic features of the important homogeneous Group 4 metallocene Ziegler catalyst systems.[1]

The interaction of transition metals with biomolecules is an essential feature of the function of a large number of chemical systems in living organisms. Very many related bioinorganic or bioorganometallic model systems have been devised, extensively studied, and published in the chemical and biological literature.[2] In contrast, very little is known about the interaction of bioorganic substrates with the very electrophilic organometallic compounds of the early transition metals.[3] At first glance this may not seem surprising since such organometallics are often hydrolytically unstable, but some important potential pharmaceutical applications of such systems may be within reach, such as the use of titanocene- or vanadocene-derived compounds in cancerostatic medication.[4] Therefore, it should be worthwhile to try to overcome this obstacle and search for ways of connecting the hydrophobic Group 4 organometallics with suitable examples from the world of the hydrophilic biomolecules. We have followed several complementary strategies to achieve such a combination[5] and have now found a simple route for the preparation of novel Group 4 metallocene cation systems that bear amino acid- or oligopeptide-derived σ-ligands at the electrophilic early transition metal center. First representative examples of this synthetic development are described in this article.

Results and Discussion

Synthesis of the Functionalized Metallocene Cations: We decided to try to construct the functional group that serves to connect the early transition metal and the amino acid or oligopeptide moiety, respectively, in the course of the reaction step that brings the two components together. For that purpose we have converted valine methyl ester to the corresponding isocyanate **2a** by treatment with trichloromethyl chloroformate ("phosgene dimer")[6] and then combined it with $[Cp_2ZrCH_3(thf)]^+BPh_4^-$ (**1**) in a 1:1 molar ratio in dichloromethane at −30 °C (Scheme 1). Bringing this mixture to room temperature resulted in a clean reaction. The zirconium-bound methyl group is sufficiently nucleophilic to add to the



Scheme 1. Reaction of **1** (the cation is shown; the anion is BPh_4^-) with **2a** to make **3a**.

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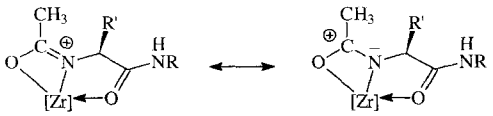
  0947-6539/97/0309-1521 $ 17.50+.50/0

isocyanate carbon atom with C–C bond formation. The cationic addition product was isolated in >95% yield. The metallated *N*-acetylvaline ester thus formed is bound to the zirconium center through nitrogen, the *N*-acetyl oxygen, and the ester carbonyl oxygen atom. This is evident from the absence of any NH feature in the ^{1}H NMR and the IR spectra of the resulting product **3a** and the observation of the corresponding ^{13}C NMR acetyl C=O resonance at a very high δ value of 180.6. The connectivity of the complex framework (Scheme 2) was secured by 2D NMR spectroscopy by means of the results of the ^{13}C/^{1}H gradient heteronuclear multiple bond correlation experiment (GHMBC).[7] This indicates that the ^{13}C NMR resonance at δ 185.2 arises from the ester carbonyl carbon, which also interacts with the electrophilic zirconocene moiety.



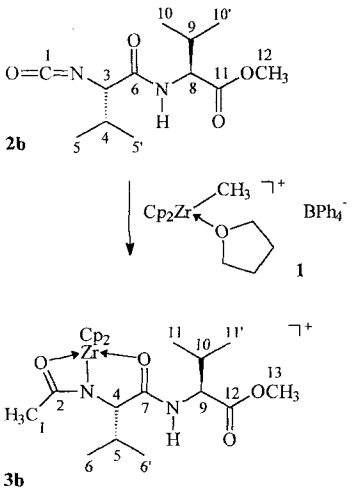
A **B**

Scheme 2. Connectivity of the framework in **3**.

Complex **3a** thus exhibits a very rigid structure that is characterized by a metallabicyclic framework. Three of the heteroatoms introduced by the *N*-acetylvaline ester moiety have become bound to the zirconium center, namely the *N*-acetyl oxygen and nitrogen atoms and, in addition, the ester carbonyl oxygen atom.

The framework contains a single (valine-derived) chiral center, at carbon atom C4. This leads to diastereotopic splitting of both the isopropyl methyl groups (^{1}H/^{13}C NMR signals at δ = 1.12, 1.06/19.1, 18.8) and the Cp ligands (^{1}H/^{13}C NMR resonances: δ = 6.34, 6.17/116.2, 115.8 in CD_2Cl_2 at ambient temperature), as expected.

We next employed this reaction scheme to attach a dipeptide-derived moiety to the zirconocene cation. For that purpose the isocyanate **2b** derived from dipeptide ester H–Val–Val–OMe was prepared (Scheme 3).[6, 8] Compound **2b** was then treated with **1** in dichloromethane. We tried to follow the course of the reaction by carrying it out in CD_2Cl_2 solution under direct ^{1}H NMR observation starting at −30 °C. A reaction between the reagents **1** and **2b** sets in instantaneously, but it leads to a very complicated mixture of as yet unidentified products. This probably indicates that the $[Cp_2ZrCH_3]^+$ ion initially makes contact with a variety of nucleophilic sites of **2b**. With increasing temperature the NMR spectra become less complicated and eventually a single reaction product (**3b**) is developed that is isolated in near-quantitative yield when the reaction is carried out on a preparative scale.



2b **1** **3b**

Scheme 3. Reaction of isocyanate **2b** with **1**.

The NMR spectra of **3b** again suggest the presence of an annulated set of four- and five-membered chelates involving coordination of the N-terminus of the dipeptide. According to the ^{13}C NMR spectrum of **3b** the *N*-acetyl carbonyl group and the C=O group of the N-terminal valyl moiety are coordinated to zirconium. The ^{13}C NMR resonances of the corresponding carbonyl carbon atoms C2 and C7 appear at δ = 180.8 and 180.4, respectively, whereas the ester group is noncoordinating (^{13}C NMR carbonyl signal at δ = 170.1 in CD_2Cl_2).

Accordingly, there are two pairs of diastereotopic isopropyl methyl groups of the two valine units (^{13}C NMR signals at δ = 19.7, 19.1, 18.3, 18.0) and a pair of diastereotopic Cp ligands at zirconium (^{1}H/^{13}C NMR: δ = 6.28, 6.13/115.7, 114.9).

X-Ray Crystal Structure Analysis: Complex **3b** was dissolved in bromobenzene and pentane was allowed to diffuse into this solution during 24 h at ambient temperature in a closed system of two connected Schlenk flasks. During this time single crystals of **3b** developed that were used for an X-ray crystal structure analysis. The overall structural picture as deduced from the NMR analysis (see above) was confirmed by the results of the X-ray crystal structure investigation. In the cation a zirconocene unit [Cp(centroid)-Zr-Cp(centroid) angle 129.2°] is present that has the *N*-acetylated dipeptide ester coordinated in the typical bent metallocene σ-ligand plane that bisects the Cp-Zr-Cp angle. All three metallocene orbitals that are available for establishing a bond to incoming ligands in that particular plane seem to be involved, which means that three binding sites of the peptide backbone are used to establish the bonding contact between the organometallic Cp_2Zr template and the organic oligopeptide σ-ligand framework.

The zirconium center is strongly bound to the *N*-acetyl nitrogen (Zr–N3 2.167(12) Å) and the corresponding acetyl oxygen atom (Zr–O1 2.185(12) Å).[9, 10] In addition, there is a strong bonding contact between zirconium and the amide carbonyl oxygen of the adjacent (i.e., C-terminal) valyl moiety (Zr–O7: 2.251(11) Å). The C-terminal valine ester carbonyl functionality is not involved in the oligopeptide coordination to zirconium (Figure 1).

The terminal oligopeptide *N*-acetyl group is (η^1-O:η^1-N)-coordinated to zirconium. This leads to a nearly coplanar arrangement of Zr, O1, C1, C2, and N3 and to a strong deviation of several characteristic bonding features from the characteristic peptide values. For the purpose of a structural comparison we have synthesized a number of related *N*-protected oligopeptide esters. We were successful in obtaining single crystals of the system Boc-Gly–Val–Ala–OMe (**4**) and have characterized this compound by an X-ray crystal structure analysis (Figure 2). The structural parameters of the backbone section of **4**, ranging

0947-6539/97/0309-1522 $ 17.50+.50/0 *Chem. Eur. J.* **1997**, *3*, No. 9

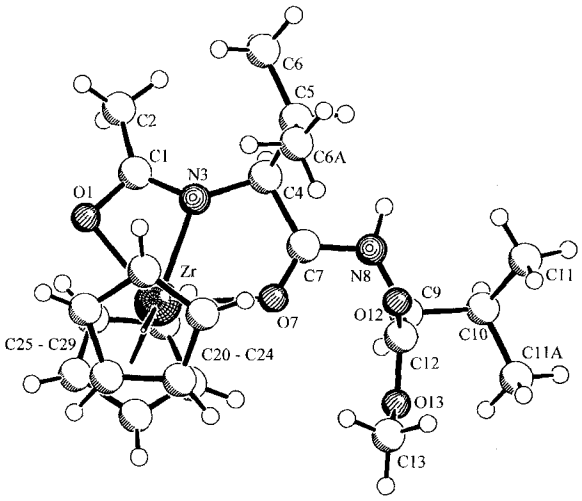


Figure 1. A view of the molecular geometry of **3b** (cation part only) with (unsystematic) atom numbering scheme. Selected bond lengths (Å) and angles (°): Zr–O1 2.185(12), Zr–N3 2.167(12), Zr–O7 2.251(11), C1–O1 1.35(2), C1–C2 1.45(2), C1–N3 1.32(2), N3–C4 1.48(2), C4–C7 1.53(2), C7–O7 1.22(2), C7–N8 1.33(2), N8–C9 1.42(2), C9–C12 1.48(3), C12–O12 1.19(2), C12–O13 1.31(2), O13–C13 1.43(2); Zr-O1-C1 94.4(10), Zr-N3-C1 96.3(10), Zr-O7-C7 122.2(11), O1-Zr-N3 58.8(5), O1-Zr-O7 125.9(5), N3-Zr-O7 67.4(5), O1-C1-N3 106.4(14), C1-N3-C4 128.1(13), N3-C4-C7 99.7(13), C4-C7-O7 121(2), C4-C7-N8 121(2), O7-C7-N8 118(2), N8-C9-C12 111(2), C9-C12-O12 127(2), C9-C12-O13 112(2), O12-C12-O13 122(2), C12-O13-C13 119(2).

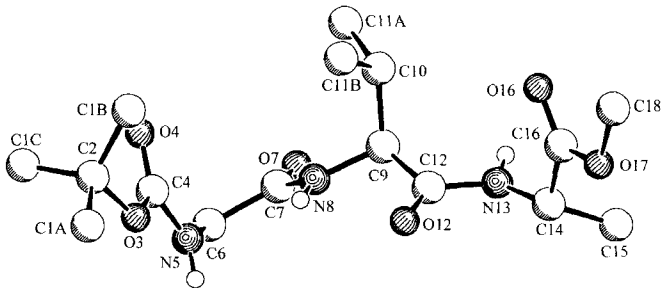


Figure 2. A projection of the molecular geometry of Boc-Gly–Val–Ala–OMe (**4**) with (unsystematic) atom numbering scheme. Selected bond lengths (Å) and angles (°): C2–O3 1.480(3), O3–C4 1.342(3), C4–O4 1.201(3), C4–N5 1.351(3), N5–C6 1.445(3), C6–C7 1.521(3), C7–O7 1.229(3), C7–N8 1.326(3), N8–C9 1.453(2), C9–C12 1.518(3), C12–O12 1.224(2), C12–N13 1.348(3), N13–C14 1.443(3), C14–C16 1.519(3), C16–O16 1.180(3), C16–O17 1.300(3), O17–C18 1.473(4); C2-O3-C4 120.4(2), O3-C4-O4 126.6(2), O3-C4-N5 109.3(2), O4-C4-N5 124.0(2), C4-N5-C6 120.4(2), N5-C6-C7 115.0(2), C6-C7-O7 120.1(2), C6-C7-N8 116.2(2), O7-C7-N8 123.6(2), C7-N8-C9 123.3(2), N8-C9-C12 108.1(2), C9-C12-O12 122.2(2), C9-C12-N13 114.2(2), O12-C12-N13 123.6(2), C12-N13-C14 121.8(2), N13-C14-C16 109.3(2), C14-C16-O16 124.0(2), C14-C16-O17 112.7(2), O16-C16-O17 123.3(2), C16-O17-C18 115.4(2).

from O7, C7, N8 all the way to the methyl ester terminus, serve to provide suitable model values for a comparison with the cationic "zirconated" oligopeptide system **3b**, and characterization of the structural variation introduced by the coordinative interaction of the peptide framework with the electrophilic metallocene cation moiety.

Complex **3b** contains a five-membered chelate ring at zirconium involving the nitrogen atom N3, the carbon centers C4, C7, and the carbonyl oxygen atom O7 (see Figure 1). The corresponding amide functionality (involving C4, C7, O7, N8) is planar and in a typical *trans* arrangement. Therefore, it is not unexpected that the characteristic structural values of this part of the molecule **3b** do not deviate too much from the typical peptide values [**3b**: N3–C4 1.48(2), C4–C7 1.53(2), C7–N8 1.33(2), C7–O7 1.22(2) Å; for a direct comparison, **4** (Figure 2): N8–C9 1.453(2), C9–C12 1.518(3), C12–N13 1.348(3), C12–O12 1.224(2) Å; corresponding bond angles of the metallocene peptide cation **3b**: C4-C7-O7 121(2)°, C4-C7-N8 121(2)°, O7-C7-N8 118(2)°, C7-N8-C9 120(2)°, of the peptide **4**: C9-C12-O12 122.2(2)°, C9-C12-N13 114.2(2)°, O12-C12-N13 123.6(2)°, C12-N13-C14 121.8(2)°]. The set of chelate angles of **3b** is completed by a large angle at the tricoordinate nitrogen (Zr-N3-C4 127.9(10)°) and a rather small angle at C4 (N3-C4-C7 99.7(13)°). The C7-O7-Zr angle is 122.2(11)° and the remaining five-membered ring angle at zirconium (O7-Zr-N3) is 67.4(5)°. It must be emphasized that coordination of the C7–O7 carbonyl group to zirconium does not lead to any significant reduction in the length of the C=O double bond (**3b**: C7–O7 1.22(2) Å vs. **4**: C12–O12 1.224(2) Å).

The situation at the annulated four-membered chelate ring that completes the coordination sphere at zirconium in complex **3b** is distinctly different. Here, the coordination of the *N*-acetyl group leads to a significant reduction of the bond order of the C=O linkage. The C1–O1 distance is 1.35(2) Å, which corresponds to an increase in the C=O bond length of >0.1 Å induced by coordination.[11] The bond angles inside the planar four-membered ring system amount to 58.8(5)° (N3-Zr-O1), 94.4(10)° (Zr-O1-C1), 106.4(14)° (O1-C1-N3), and 96.3(10)° (C1-N3-Zr). It should be noted that the C1–N3 bond (1.32(2) Å) inside this structural subunit of **3b** is not reduced compared with that of a typical corresponding amide C(sp^2)–N(sp^2) linkage[12] (cf. **4**: C7–N8 1.326(3) Å). It appears that the (η^1-O1: η^1-N3)-*N*-acetyl coordination to zirconium in **3b** can probably be described to some approximation by a situation involving the resonance hybrid structures **A** and **B** (Scheme 2), which provides an ample description of the experimentally observed significant reduction of the *N*-acetyl C=O bond order while the *N*-acetyl C···CN bond order is approximately maintained. In contrast, the π-bond of the adjacent amide carbonyl group (i.e., the C7–O7 double bond in Figure 1) is apparently not affected by the strong coordination of the carbonyl oxygen to zirconium by its lone pair. This dative η^1-O bond (O7 → Zr), which complements the coordination sphere of the zirconium cation, apparently does not affect the structural properties (and probably the chemical properties either) of the O7-C7-N8 amide linkage, whereas the η^1-O:η^1-N coordination substantially alters the features of the adjacent O1-C1-N3 amide functionality.

The structural features of the C-terminus of the peptide moiety in **3b** are very similar to those observed for the oligopeptide derivative **4**. The C12-centered ester moiety in **3b** is rotated relative to the main plane of the oligopeptide framework (dihedral angles C7-N8-C9-C12 −64(2)°, N8-C9-C12-O12 −30(3)°).

Conclusion

This work has shown that amino acid and oligopeptide ligand systems can be readily attached to very electrophilic Group 4 metallocene cations such as the Cp_2ZrX^+ system. The derived cationic complexes are moderately stable, even when the newly

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attached σ-type ligand systems contain a high degree of functionality. The synthesis of the examples of the class of compounds described in this paper has been quite specific as it requires the conversion of the N-terminus of the dipeptide to an isocyanate functional group prior to the attachment of this ligand system to the transition metal center. However, this specific synthesis has, to the best of our knowledge, made such cationic early transition metal–oligopeptide systems available for the first time. Now that the existence and relative kinetic stability of such complexes has been demonstrated it should be easy to devise more general entries to this type of compound, starting directly from readily available, if not ubiquitous, oligopeptide derivatives, and to develop the chemistry and catalytic applications of these interesting new metallocene–oligopeptide systems. Such a development is being pursued in our laboratory and further progress in this area will be reported shortly.

Experimental Section

General information: Reactions with organometallic reagents or substrates were carried out in an inert atmosphere (argon) using Schlenk type glassware or in a glovebox. Solvents were dried and distilled under argon prior to use. The following instrumentation was used for physical and spectroscopic characterization of the compounds: Bruker AC 200 P, ARX 300 and Varian Unity Plus 600 NMR spectrometers; Nicolet 5 DXC FT-IR spectrometer; Finnigan MAT 8230 mass spectrometer (EI, 70 eV); elemental analyses were carried out with a Foss-Heraeus CHNO-Rapid elemental analyzer, optical rotations were measured with a Perkin–Elmer 241 MC polarimeter; melting points were determined by differential scanning calorimetry on a DuPont DSC 910; the X-ray crystal structures were analysed with Enraf–Nonius CAD 4 or MACH 3 diffractometers (programs used included SHELX 86, SHELX 93, and SCHAKAL). Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-100396. Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: Int. code +(1223) 336-033; e-mail: deposit@chemcrys.cam.ac.uk).

The organometallic reagent $[Cp_2ZrCH_3(thf)]^+BPh_4^-$ (**1**) was prepared according to a literature procedure.[13] The isocyanates **2a** and **2b** have been described previously[6, 14] but were prepared here by variations of the literature procedures employing "phosgene dimer" as a reagent.

***N*-Carbonylvaline methyl ester (2a)**:[6] Trichloromethyl chloroformate ("phosgene dimer", 26.1 mL, 42.8 g, 206 mmol) was added to a solution of valine methyl ester hydrochloride (17.3 g, 103 mmol) in toluene (ca. 200 mL). The mixture was heated under reflux for 1 h and then left at ambient temperature overnight. The product was isolated by distillation (b.p. = 51 °C at 4 mbar) to yield 15.2 g (95%) of the valine-ester-derived isocyanate as a colorless liquid, with a pungent odor, that was used without further purification. ^{1}H NMR ($CDCl_3$, 200.1 MHz): δ = 3.91 (d, ^3J = 3.8 Hz, 1H, N–CH), 3.77 (s, 3H, OCH_3), 2.20 (dqq, ^3J = 3.8 Hz, ^3J = 6.8 Hz, 1H, *i*-propyl CH), 0.99 and 0.86 (both d, ^3J = 6.8 Hz, 2 × 3H, *i*-propyl CH_3); ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 171.1 (CO_2Me), 126.8 (NCO), 62.9 (*C*OCH), 52.6 (OCH_3), 31.5, 19.2 and 16.1 (iC_3H_7); IR (film): $\tilde{\nu}$ = 2968 (vs), 2934 (vs), 2877 (s), 2251 (vs, OCN), 1746 (vs, COO), 1438 (vs), 1267 (vs), 1216 (vs), 1000 (vs), 892 (s), 771 (s) cm^{-1}.

Preparation of 3a: A solution of the isocyanate **2a** (157 mg, 1.00 mmol) in CH_2Cl_2 (25 mL) was mixed with **1** (628 mg, 1.00 mmol) in CH_2Cl_2 (25 mL) at −30 °C. The mixture was allowed to warm to room temperature with stirring. Solvent was removed in vacuo. The residue was washed with pentane to give **3a** as a white powdery solid, yield 680 mg (95%), m.p. 29 °C (decomp.), $[\alpha]_D$ = −14 (c = 0.2, CH_2Cl_2). Anal. calcd for $C_{42}H_{44}BNO_3Zr$ (712.8): C 70.77, H 6.22, N 1.96; found C 68.72, H 6.31, N 1.91; ^{1}H NMR (CD_2Cl_2, 599.8 MHz): δ = 6.34 and 6.17 (both s, 5H, Cp), 4.31 (d, ^3J = 3.5 Hz, 1H, 4-H), 3.99 (s, 3H, 8-H), 2.29 (m, 1H, 5-H), 2.01 (s, 3H, 1-H), 1.12 and 1.06 (both d, ^3J = 7.0 Hz, 3H, 6- and 6′-H); $[BPh_4]^-$: 7.34 (m, 8H, *o*-H), 7.06 (m, 8H, *m*-H), 6.94 (m, 4H, *p*-H); ^{13}C NMR (CD_2Cl_2, 150.8 MHz): δ = 185.2 (C7), 180.6 (C2), 116.2 and 115.8 (Cp), 67.9 (C4), 58.2 (C8), 34.3 (C5), 20.8 (C1), 19.1 and 18.8 (C6, C6′); $[BPh_4]^-$: 164.4 (q, $^2J_{CB}$ = 49 Hz, *ipso*), 136.3 (*o*), 126.1 (*m*), 122.1 (*p*); 2D NMR (GHMBC, giving the long range correlation, CD_2Cl_2, 150.8/599.8 MHz): δ = 185.2/3.99 (C7/8-H), 180.6/2.01 (C2/1-H), 116.2/6.34 (Cp/Cp-H), 115.8/6.17 (Cp′/Cp′-H), 67.9/1.12 and 1.06 (C4/6- and 6′-H), 58.2/3.99 (C8/8-H), 34.3/1.12 and 1.06 (C5/6- and 6′-H), 19.1 and 18.8/1.12 and 1.06 (C6 and C6′/6- and 6′-H, cross peak not resolved); $[BPh_4]^-$: 164.4/7.34 (*ipso*/*p*-H), 164.4/7.06 (*ipso*/*o*-H), 136.3/7.34 (*o*/*o*-H), 136.3/7.06 (*o*/*m*-H), 136.3/6.94 (*o*/*p*-H), 126.1/7.34 (*m*/*o*-H), 126.1/7.06 (*m*/*m*-H), 126.1/6.94 (*m*/*p*-H), 122.1/7.34 (*p*/*o*-H), 122.1/7.06 (*p*/*m*-H).

***N*-Carbonylvalylvaline methyl ester (2b)**:[14] A solution of *N*-trimethylsilylvaline methyl ester (3.10 g, 15.3 mmol)[15] in pentane (25 mL) was added at −10 °C under argon to a solution of (*S*)-2-isocyanato-2-isopropylacetyl chloride[16] (2.16 mL, 2.48 g, 15.3 mmol) in pentane (25 mL). The mixture was allowed to warm up to room temperature and stirred overnight. The supernatant liquid was decanted from the white precipitate formed. The solid was washed with a small volume of pentane, then dried in vacuo to yield 3.92 g (quant.) of **2b**, $[\alpha]_D$ = + 6 (c = 0.36, CH_2Cl_2). Anal. calcd for $C_{12}H_{20}N_2O_4$ (256.3): C 56.24, H 7.86, N 10.93; found C 55.29, H 7.96, N 10.49; ^{1}H NMR ($CDCl_3$, 200.1 MHz): δ = 6.65 (br d, ^3J = 8.6 Hz, 1H, 7-H), 4.49 (dd, ^3J = 8.6 Hz, ^3J = 4.8 Hz, 1H, 8-H), 4.02 (d, ^3J = 3.4 Hz, 1H, 3-H), 3.71 (s, 3H, 12-H), 2.32 (dqq, ^3J = 3.4 Hz, ^3J = 6.8 Hz, ^3J = 6.8 Hz, 1H, 4-H), 2.16 (dqq, ^3J = 3.4 Hz, ^3J = 4.8 Hz, ^3J = 6.8 Hz, 1H, 9-H), 1.36 (d, ^3J = 6.8 Hz, 3H, 5-H), 0.89 (m, 9H, 5′-, 10- and 10′-H); ^{13}C NMR ($CDCl_3$, APT, 50.3 MHz): δ = 171.9 and 169.0 (C6 and C11), 125.7 (C1), 64.8 (C3), 57.4 (C8), 52.2 (C12), 32.3 and 31.1 (C4 and C9), 19.8, 18.8, 17.7, and 16.0 (C5, C5′, C10 and C10′); IR (CH_2Cl_2): $\tilde{\nu}$ = 3413 (m, NH), 3359 (br, NH), 3056 (m), 2969 (s), 2934 (m), 2876 (m), 2245 (vs, OCN), 1741 (vs, COO), 1684 (vs, CON), 1520 (s, CON), 1437 (m), 1266 (vs), 1211 (s), 1152 (m) cm^{-1}.

Preparation of 3b: A solution of **1** (313 mg, 0.5 mmol) in CH_2Cl_2 (25 mL) was combined with a solution of the isocyanate **2b** (128 mg, 0.5 mmol) in CH_2Cl_2 (25 mL) at −30 °C. The mixture was allowed to warm to room temperature and then stirred for another 2 h. Solvent was removed in vacuo, the residue washed with some pentane, and dried in vacuo to yield 405 mg (quant.) of **3b**, m.p. 45 °C (decomp), $[\alpha]_D$ = −71 (c = 0.18, CH_2Cl_2). Anal. calcd for $C_{47}H_{53}BN_2O_4Zr$ (812.0): C 69.52, H 6.58, N 3.45; found C 68.46, H 6.20, N 4.06; ^{1}H NMR (CD_2Cl_2, 200.1 MHz): δ = 6.28 and 6.13 (s, each 5H, Cp), 4.42 (dd, ^3J = 8.2 Hz, ^3J = 4.8 Hz, 1H, 9-H), 4.20 (d, ^3J = 3.7 Hz, 1H, 4-H), 3.85 (s, 3H, 13-H), 3.73 (br, 1H, 8-H), 2.18 (m, 2H, 5- and 10-H), 1.97 (s, 3H, 1-H), 1.06 (m, 12H, 6-, 6′-, 11- and 11′-H); $[BPh_4]^-$: 7.36 (m, 8H, *o*-H), 7.06 (m, 8H, *m*-H), 6.94 (m, 4H, *p*-H); ^{13}C NMR (CD_2Cl_2, 50.3 MHz): δ = 180.8 and 180.4 (C2 and C7), 170.1 (C12), 115.7 and 114.9 (Cp), 67.7 (C4), 60.3 (C9), 53.2 (C13), 35.1 (C5), 30.6 (C10), 20.7 (C1), 19.7, 19.1, 18.3 and 18.0 (C6, C6′, C11 and C11′); $[BPh_4]^-$: 164.5 (q, $^2J_{CB}$ = 49 Hz, *ipso*), 136.3 (*o*), 126.0 (*m*), 122.2 (*p*); IR (CH_2Cl_2): $\tilde{\nu}$ = 3371 (br, NH), 3054 (m), 2983 (m), 1744 (s, COO), 1710 (m, CON), 1598 (s, CON), 1437 (m), 1426 (m), 1265 (vs), 1016 (m), 816 (s), 737 (vs), 705 (vs) cm^{-1}. X-ray crystal structure analysis: Crystals were obtained from bromobenzene/pentane by the diffusion method. $C_{47}H_{53}BN_2O_4Zr$; M = 811.94 g mol^{-1}; triclinic space group; $P\bar{1}$ (No. 1); cell constants: a = 9.657(6) Å, b = 11.080(2) Å, c = 11.452(2) Å; α = 64.57(2)°; β = 74.58(4)°; γ = 72.29(4)°; V = 1041.1(7) Å^3; T = −50 °C; crystal size: 0.40 × 0.20 × 0.20 mm; Z = 1; ρ_{calcd} = 1.295 g cm^{-3}; λ = 0.71073 Å; $[\sin\theta/\lambda]_{max}$ = 0.59 Å^{-1}; μ = 0.309 mm^{-1}; 3714 reflections measured ($\pm h$, $+k$, $\pm l$); 3714 independent and 1604 observed reflections; 487 refined parameters; R = 0.078; wR^2 = 0.177.

Preparation of 4: A sample of the protected dipeptide Boc-Gly-Val-OH[8] (3.56 g, 12.9 mmol) was dissolved in CH_2Cl_2 (80 mL). Hydroxybenzotriazole (2.47 g, 16.1 mmol) and dicyclohexylcarbodiimide (3.32 g, 16.1 mmol) were added. After 20 min the resulting precipitate was removed by filtration and the clear filtrate combined with a suspension of alanine methyl ester hydrochloride (1.80 g, 12.9 mmol) and triethylamine (1.72 mL, 1.25 g, 12.4 mmol) in CH_2Cl_2 (20 mL). The mixture was stirred for 2 h and then successively washed with 120 mL portions of 2M hydrochloric acid (× 3), water, 5% sodium bicarbonate solution, and water. The organic layer was dried over anhydrous magnesium sulfate, the solvent removed in vacuo, and

0947-6539/97/0309-1524 $ 17.50+.50/0 Chem. Eur. J. 1997, 3, No. 9

the crude product (2.41 g) recrystallized from methyl acetate/petrol to yield 1.87 g (40%) of **4**, m.p. = 149 °C, $[\alpha]_D = -20$ ($c = 0.1$, CH_2Cl_2). Anal. calcd for $C_{16}H_{29}N_3O_6$ (359.4): C 53.47, H 8.13, N 11.69; found C 53.98, H 8.10, N 11.81; ^{1}H NMR (CD_2Cl_2, 599.8 MHz, numbering as in Figure 2): $\delta = 6.87$ (br, 2H, N8–H and N13–H), 5.35 (br, 1H, N5-H), 4.52 (dq, $^3J = 7.2$ Hz, 1H, 14-H), 4.33 (dd, $^3J = 8.8$ Hz, $^3J = 6.7$ Hz, 1H, 9-H), 3.81 (m, 2H, 6-H and -H'), 3.71 (s, 3H, 18-H), 2.09 (m, 1H, 10-H), 1.42 (s, 9H, 1-H), 1.37 (d, $^3J = 7.2$ Hz, 3H, 15-H), 0.94 and 0.91 (d, each $^3J = 6.6$ Hz, 11-H); ^{13}C NMR (CD_2Cl_2, 150.8 MHz): $\delta = 173.4$ (C16), 171.0 and 170.0 (C7 and C12), 155.5 (C4), 80.2 (C2), 58.2 (C9), 52.6 (C18), 48.5 (C14), 44.7 (C6), 31.6 (C10), 28.4 (C1), 19.2 (C11), 18.0 (C11′ and C15, isochronous); 2D NMR (GHMBC, CD_2Cl_2, 150.8/599.8 MHz): $\delta = 173.4/4.52$ (C16/14-H), 173.4/3.71 (C16/18-H), 173.4/1.37 (C16/15-H), 171.0 and 170.0/4.33 (C7 and C12/9-H), 80.2/1.42 (C2/1-H), 58.2/2.09 (C9/10-H), 58.2/0.94 and 0.91 (C9/11- and 11′-H), 52.4/3.71 (C18/18-H), 48.1/1.37 (C14/15-H), 31.2/4.33 (C10/9-H), 31.2/0.94 and 0.91 (C10/11- and 11′-H), 28.3/1.42 (C1/1-H), 19.2 and 18.0/4.33 (C11 and C11′/9-H), 19.2 and 18.0/0.94 and 0.91 (C11 and C11′/11- and 11′-H), 18.0/4.52 (C15/14-H); IR (KBr): $\tilde{\nu} = 3406$ (m, NH), 3275 (m, NH), 2980 (w), 2963 (w), 1738 (m, COO), 1718 (s, CON), 1659 (vs, CON), 1502 (s), 1170 (m) cm^{-1}; X-ray crystal structure analysis: Single crystals were obtained from dichloromethane solution by allowing the solvent to slowly evaporate. $C_{16}H_{29}N_3O_6$; $M = 359.42$ g mol^{-1}; orthorhombic space group; $P2_12_12_1$ (No. 19); cell constants: $a = 8.435(1)$ Å, $b = 9.218(1)$ Å, $c = 26.918(4)$ Å; $V = 2093.0(5)$ Å^3; $T = -50$ °C; crystal size: $0.60 \times 0.50 \times 0.50$ mm; $Z = 4$; $\rho_{calcd} = 1.141$ g cm^{-3}; $\lambda = 1.54178$ Å; $[\sin \theta/\lambda]_{max} = 0.62$ Å^{-1}; $\mu = 0.726$ mm^{-1}; 2460 reflections measured ($-h$, $-k$, $-l$); 2460 independent and 2213 observed reflections; 243 refined parameters; $R = 0.038$; $wR^2 = 0.102$.

Acknowledgements: Financial support from the Fonds der Chemischen Industrie, the Deutsche Forschungsgemeinschaft (SFB 424), and the Wissenschaftsministerium des Landes Nordrhein-Westfalen is gratefully acknowledged.

Received: February 4, 1997 [F 601]

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