ELSEVIER

www.elsevier.nl/locate/jorganchem

Journal of Organometallic Chemistry 589 (1999) 21–28

Journal of Organometallic Chemistry

Metal complexes of biologically important ligands, Part CXVIII. Metathesis of dehydro amino acids with Fischer carbene complexes: synthesis of complexes of amino acid- and peptide-α-carbenes and of isoindoles☆

Harald Dialer, Kurt Polborn [1], Wolfgang Beck *

Institut für Anorganische Chemie der Ludwig-Maximilians-Universität München, Butenandtstraße 5-13, 81377 Munich, Germany

Received 31 March 1999

Dedicated to Professor Wolf Peter Fehlhammer on the occasion of his 60th birthday as a mark of friendship.

Abstract

Metathesis of N-protected dehydro alanine esters with Fischer carbene complexes affords α-amino acid metal carbenes $O(CH_2CH_2)_2N–C[=M(CO)_5](CO_2Me)$ (**3**) and $Ph_2C=N–C[=M(CO)_5](CO_2Et)$ (**6**) (M = Cr, Mo, W). The X-ray structural analysis of **6c** shows the dominance of the zwitterionic form $Ph_2C=N=C[M(CO)_5](CO_2Et)$ in these complexes. Labeling of peptides by the $M(CO)_5$ fragment is demonstrated by the synthesis of $Ph_2C=N–C[=Cr(CO)_5]CONHCH(CH_2Ph)CO_2Me$ (**9**). The strongly fluorescent isoindole **7** was obtained from the carbene complexes **6** and was characterized by X-ray diffraction.

Keywords: Carbene; Amino acid; Peptide; Isoindole; Group 16 metals

1. Introduction

The broad scope of the chemistry and application of organometallic complexes of transition metals with α-amino acids and peptides was recently reviewed [2]. Various α-metallated amino acids [3] may be useful for the labeling of peptides [4] and are models for intermediates in the asymmetric hydrogenation of dehydro amino acids [5].

Fischer metal carbenes are widely used reagents in organic synthesis [6]. In the field of bioorganometallic chemistry, the synthesis of amino acids starting from amino carbene complexes [7] and the synthesis of carbohydrate-modified Fischer metal carbenes [8] are important examples. Metalla dehydro amino acids, bearing a double bond between the α-carbon of the amino acid and a metal, would represent amino acid carbenes of Fischer type.

The application of amino acid carbenes could open the access to new types of compounds and natural products. Only recently one example of this type of compound having a dimethylamino- and a carboxyl-function directly attached to the carbene carbon atom was published [9]. The method used [10] for generating these metal carbenes via a tertiary amide of oxalic acid and a carbonylmetallate is not suited for naturally occurring amino acids and peptides due to the nucleophilicity and the basicity of the carbonylmetallate.

Since the classical Fischer route is not suited for the synthesis of α-carbenes of amino acids, our approach was based on an alkene metathesis [8,11] of derivatives of α,β-didehydro amino acids with classic Fischer metal carbenes.

Didehydro amino acids [12] are found in a number of biologically active peptides, e.g. in antibiotics [13], atrimycin [14], cirratiomycin [15] or in the celenamides **A–C** [16]. The C=C double bond leads to a modification in the peptide backbone due to the sp^2-hybridization of the α-carbon and can further be subject to addition of amines or thiols.

☆ For Part CXVII, see Ref. [1].

* Corresponding author.

[1] X-ray structure determination.

0022-328X/99/$ - see front matter
PII: S0022-328X(99)00296-X

2. Results and discussion

As the substrate for metathesis we first applied the dehydro amino acid **1**, which is easily available from morpholine and methyl pyruvate [17]. Heating **1** in a sealed tube with one equivalent of the appropriate Fischer carbene complexes **2a–c** [18] in toluene or THF leads to the formation of the metal carbenes **3a–c**. The yield is strongly dependent on the metal used (Scheme 1). In the case of the less reactive molybdenum and tungsten carbenes, higher temperatures or longer reaction times do not afford any increase in yield due to the thermal instability of **1**. In the ^{13}C-NMR spectra the carbene resonance of the chromium complex **3a** appears at 258.7 ppm, which compares with that of the dimethylamino derivative [9] mentioned above. The ^{13}C-NMR shifts for molybdenum compound **3b** and tungsten compound **3c** are 249.4 and 239.2 ppm, respectively. These complexes represent the first amino acid α-carbenes of molybdenum and tungsten. The ^{1}H-NMR spectra of **3a–c** show the nonequivalence of the methylene signals of the morpholine moiety arising from the mesomeric form N=C(CO_2Me)–M which is isolobal to a peptide bond.

In the IR spectra the three intensive carbonyl absorptions can be observed at about 2060, 1980 and 1926 cm^{-1} (in accordance with local C_{4v} symmetry), along with weaker ester bands at 1711 cm^{-1}.

In the search for dehydro amino acids suited for metathesis we also concentrated on Schiff base-protected dehydro amino acids. These compounds are used for the synthesis of amino acids via nucleophilic attack at the methylene carbon atom [19,20]. In addition they occur in the form of *N*-(pyridoxylidene)dehydroalanine in the biosynthesis of some amino acids e.g. of tryptophane [21].

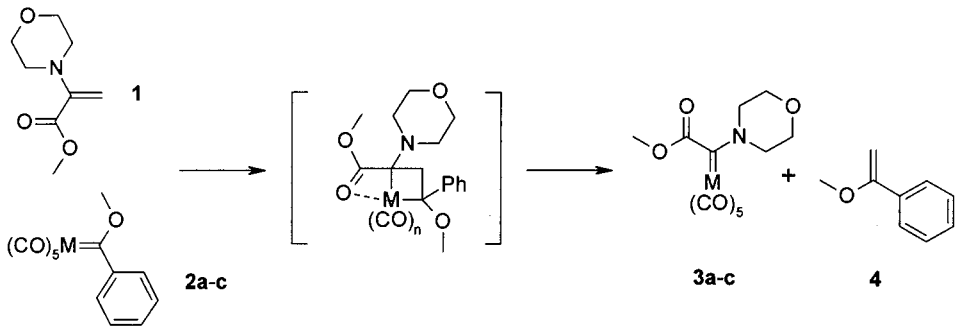
N-(Diphenylmethylene)-α,β-dehydroalanine ethyl ester **5** can be synthesized by β-elimination of water from Schiff base-protected serine esters [19] or alternatively by Hofmann elimination from ethyl-*N*-(diphenylmethylene-3-trimethylammonioalaninate iodide [20]. In an analogous procedure **5** and one equivalent of the appropriate Fischer carbene **2a–c** were reacted in toluene or THF in a sealed tube to give the red to yellow carbene complexes **6a–c** together with variable amounts (dependent on the reaction conditions) of the isoindole **7** (Scheme 2).

The ^{13}C-NMR spectra of the carbene compounds **6a–c** clearly exhibit the enhanced donor function of the diphenylmethyleneamino group compared with an amino group, resulting in a high-field shift of the carbene signal. The carbene ^{13}C-NMR shift for the complexes **6a–c** ranges from 201.7 ppm (for the chromium compound **6a**) to 183.3 ppm for the tungsten complex **6c**. Considering the proposed mechanism for the formation of the isoindole **7** (Scheme 3), this observation is not surprising as the major mesomeric contribution can be assigned to structure **A**.

The nitrile ylide structure **A** is in accordance with the spectroscopic results and was proved by X-ray analysis of the tungsten complex **6c** (Fig. 1; Tables 1 and 2).

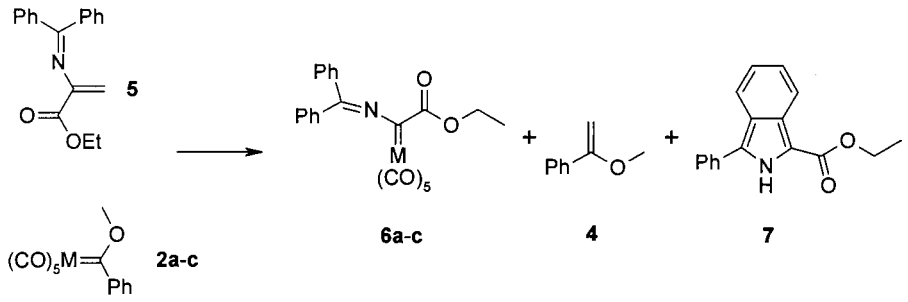
As shown in Fig. 1, the distance N(1)–C(6) of 1.253 Å is even shorter than the double bond of the Schiff base N(1)–C(7) at 1.283 Å, the angle C(6)–N(1)–C(7) being 167.3°. The negative partial charge at the metal, on the other hand, results in an elongated carbene bond W(1)–C(6) of 2.208 Å. A high contribution of a zwitterionic form was also found in amino carbene complexes L_nM–C(R)=NR_2 [22].

Carbene complexes **6a–c** (and also **3a–c**) exhibit a very high stability even in air and in aqueous solution. The ester function in these complexes can be cleaved to give the free carboxylic acids [9], bearing the possibility of a subsequent peptide synthesis. The formation of isoindole **7** involves the cleavage of the metal carbene bond to yield the free nitrile ylide **B**, ring closure (**C**)



3	M	solvent / T [°C]	time[h]	yield[%]
a	Cr	toluene / 90°	5	87
b	Mo	THF / 66°	4	57
c	W	THF / 80°	18	49

Scheme 1.



6	M	solvent / T [°C]	time[h]	yield[%]	yield of **7** [%]
a	Cr	toluene / 80°	5	49	23
b	Mo	THF / 66°	4	21	35
c	W	THF / 66°	18	27	29

Scheme 2.

and finally a sigmatropic 1,3-H shift. Some nitrile ylides generated from 2-azirines by irradiation are known to give isoindoles [23]. Fig. 2 shows the ORTEP projection of isoindole **7**, while important bond lengths and angles are gathered in Table 3. The yield of **7** can be increased by longer reaction times and higher temperatures. An almost quantitative synthesis of **7** can be performed by oxidation of the carbene complexes **6a–c** with Na_2PdCl_4 in methanol. Interestingly, derivatives of isoindole, usually synthesized by a multistep reaction via ring contraction from 1,4-benzodiazepines [24], are applied as appetite suppressants [25].

The described metathesis can also be performed using dehydropeptides. Reaction of the unsaturated dipeptide **8** (available from L-seryl-L-phenylalaninemethylester) with the Fischer carbene **2a** in toluene at 80°C leads to the formation of the pentacarbonyl chromium-labeled dipeptide **9** (Scheme 4).

In the ^{13}C-NMR spectra, the carbene resonance of the peptide complex **9** appears at 202.0 ppm, which is in accordance with the ^{13}C shift of the amino acid carbene **6a** (201.7 ppm). The CO-carbon signals appear at 217.8 ppm for *cis*-CO and at 224.7 ppm for *trans*-CO, respectively. In the IR spectra the C≡O absorptions at 2061 and 1941 cm^{-1} dominate the spectra compared with the amide and ester absorptions, which proves peptide metal carbenes like **9** to be very well suited as biomarkers. In addition, the corresponding isoindole **10** (identified by its typical fluorescence and its FAB mass spectrum ($m/z = 398$)) is formed along with a red compound not yet identified.

3. Conclusions

Using metathesis reactions the pentacarbonyl metal fragment (metal = Cr, Mo, W) can be attached to the α-carbon atom of N-protected α-amino acids. Labeling of peptides by the easily detected metal pentacarbonyl fragment is clearly demonstrated by the synthesis of a N-protected, $Cr(CO)_5$-containing dipeptide $Ph_2C{=}N{-}C[{=}Cr(CO)_5]CONHCH(CH_2Ph)CO_2CH_3$ and a straightforward synthesis of isoindoles from the carbene complexes **6** is presented.

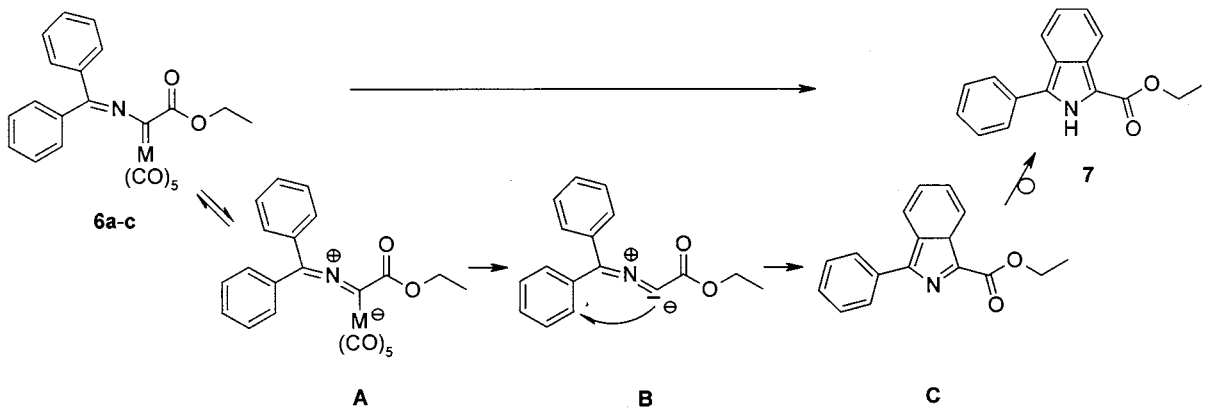
4. Experimental

THF and toluene were distilled from sodium benzophenone ketyl under argon. Chromatographic purification of the metal carbenes was performed under argon on previously degassed silica gel 60, 230–400 mesh (Merck). Chromatographic solvents were distilled and degassed by bubbling argon through them for 10 min prior to use. NMR measurements were recorded on Jeol GSX 270 or Jeol EX 400 spectrometers. IR analyses were obtained on a Nicolet 520 FT-IR spectrometer. Mass spectra were recorded on a Finnigan MAT 90 spectrometer.

Pentacarbonyl [(methoxy) phenylcarbene] chromium-(0), -molybdenum(0) and -tungsten(0) (**2a–c**) [18], dehydro amino acids **1** [17] and **5** [19,20] and *N*-diphenylmethylene-L-seryl-L-phenylalanine methylester [26] were prepared according to literature procedures.

4.1. General procedure for the synthesis of complexes *3a–c*

To a 0.1 M solution of the dehydro amino acid **1** in the solvent indicated one equivalent of the appropriate Fischer carbene **2a–c** is added under argon, and the solution is heated (temperature see Scheme 1) in an ace® pressure tube until TLC (silica gel, 3:1 hexane–ethyl acetate) shows the consumption of **1**. The solvent is removed at reduced pressure and the crude reaction mixture chromatographed on silica gel with 3:1 hex-



Scheme 3.

ane–ethyl acetate. Typically, the red first-eluted fraction contains the starting metal carbene and α-methoxystyrene **4**, while the yellow second one contains the amino acid carbenes **3a**–**c**.

*4.1.1. Pentacarbonyl[(methoxycarbonyl)(morpholino)-methylene]chromium(0) (**3a**)*

To 257 mg (1.50 mmol) of **1** in 15 ml of toluene 468 mg (1.50 mmol) of pentacarbonyl(methoxyphenylmethylene)chromium(0) (**2a**) are added and the mixture is heated to 90°C under argon for 5 h. Column chromatography (3:1 hexane–ethyl acetate) yields 456 mg (87%) of the carbene **3a**, which was recrystallized from hexane at −30°C (yellow needles).

^{1}H-NMR ($CDCl_3$, 270 MHz): $\delta = 3.63$ (t, 2H, $^3J =$ 4.7 Hz, C$\underline{H}_2$), 3.78 (t, 2H, $^3J = 4.7$ Hz, C$\underline{H}_2$), 3.87 (s, 3H, O–C$\underline{H}_3$), 4.00 (t, 2H, $^3J = 4.8$ Hz, C$\underline{H}_2$), 4.32 (t, 2H, $^3J = 4.8$ Hz, C$\underline{H}_2$). ^{13}C-NMR ($CDCl_3$): $\delta = 52.0$ (O–$\underline{C}H_3$), 58.7 ($\underline{C}H_2$), 59.0 ($\underline{C}H_2$), 67.4 ($\underline{C}H_2$), 67.6 ($\underline{C}H_2$), 170.0 (C=O_{ester}), 216.2 (C=O_{cis}), 222.3 (C=O_{trans}), 258.7 (C=Cr). IR (KBr cm^{-1}): 2061.2 (s), 1988.9 (m), 1957.0 (vs), 1926.9 (vs) [ν(C≡O)], 1711.0 (m) [ν(C=O)]. $C_{12}H_{11}CrNO_8$ (349.22) Calc.: C 41.27, H 3.17, N 4.01; Found: C 41.31, H 3.13, N 3.90%.

*4.1.2. Pentacarbonyl[(methoxycarbonyl)(morpholino)-methylene]molybdenum(0) (**3b**)*

To 257 mg (1.50 mmol) of **1** in 15 ml of THF 534 mg (1.50 mmol) of pentacarbonyl(methoxyphenylmethylene)molybdenum(0) **2b** are added and the mixture is heated to 66°C under argon for 4 h. Column chromatography (3:1 hexane–ethyl acetate) yields 336 mg (57%) of the carbene **3b**, which was recrystallized from hexane at −30°C (yellow needles).

^{1}H-NMR ($CDCl_3$, 270 MHz): $\delta = 3.51$ (s, br, 2H, C$\underline{H}_2$), 3.68 (s, br, 2H, C$\underline{H}_2$), 3.79 (s, 3H, O–C$\underline{H}_3$), 3.91 (s br, 2H, C$\underline{H}_2$), 3.51 (s br, 2H, C$\underline{H}_2$). ^{13}C-NMR ($CDCl_3$): $\delta = 51.9$ (O–$\underline{C}H_3$), 58.7 ($\underline{C}H_2$), 59.0 ($\underline{C}H_2$), 67.5 ($\underline{C}H_2$), 67.6 ($\underline{C}H_2$), 170.0 (C=O_{ester}), 216.1 (C=O_{cis}), 222.3 (C=O_{trans}), 249.4 (C=Mo). IR (KBr cm^{-1}): 2060.7 (s), 1990.7 (m), 1958.5 (vs), 1921.9 (vs) [ν(C≡O)], 1710.9 (m) [ν(C=O)]. $C_{12}H_{11}MoNO_8$ (393.16) Calc.: C 36.66, H 2.82, N 3.56; Found: C 36.40, H 3.60, N 3.89%.

*4.1.3. Pentacarbonyl[(methoxycarbonyl)(morpholino)-methylene]tungsten(0) (**3c**)*

To 257 mg (1.50 mmol) of **1** in 15 ml of THF 666 mg (1.50 mmol) of pentacarbonyl(methoxyphenylmethylene)tungsten(0) **2c** are added and the mixture is heated to 80°C under argon for 18 h. Column chromatography (3:1 hexane–ethyl acetate) yields 354 mg

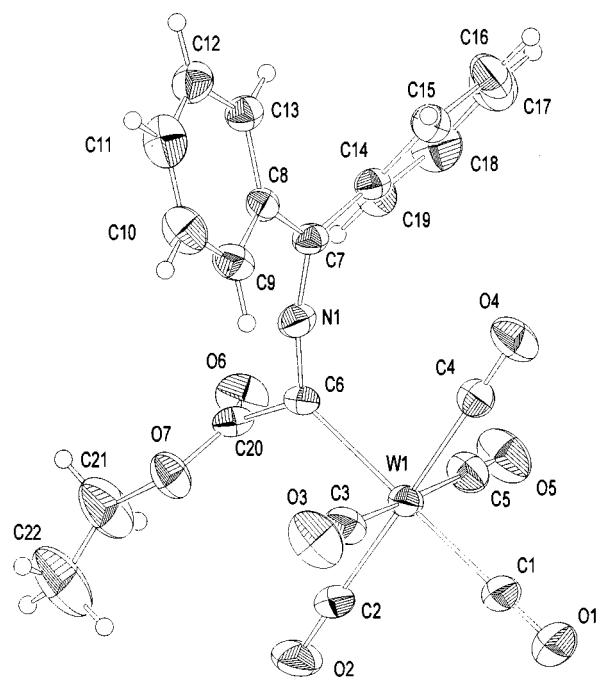


Fig. 1. ORTEP projection of the tungsten complex **6c** with the atom numbering scheme.

Table 1
Crystallographic data for **6a** and **7** [a]

	6a	**7**
Molecular formula	$C_{22}H_{15}NO_7W$	$C_{17}H_{15}NO_2$
Formula weight	589.20	265.30
a (Å)	9.8195(11)	26.403(2)
b (Å)	22.021(5)	7.281(3)
c (Å)	10.866(2)	14.857(3)
α (°)	90.00(2)	90.00(2)
β (°)	108.456(14)	95.429(14)
γ (°)	90.00(2)	90.00(2)
V (Å^3)	2228.7(7)	2843.4(12)
Z	4	8
Crystal system	Monoclinic	Monoclinic
Space group	$P2_1/n$	$C2/c$
Absorption coefficient μ (mm^{-1})	5.225	0.081
Density ρ (g cm^{-3})	1.756	1.239
Crystal size (mm)	$0.40\times0.33\times0.27$	$0.53\times0.43\times0.27$
Diffractometer	Enraf Nonius CAD 4	Enraf Nonius CAD 4
Radiation	Mo–K_α ($\lambda=0.71073$ Å)	Mo–K_α ($\lambda=0.71073$ Å)
Temperature (K)	293(2)	293(2)
Scan range (°)	$0.90+0.45$ tgθ	$0.69+0.51$ tgθ
θ Limits (°)	2.18–23.97	2.75–23.96
Reflections collected	3712	2324
Independent reflections	3492 ($R_{int}=0.0509$)	2218 ($R_{int}=0.0078$)
Absorption correction	Semi-empirical from Ψ-scans	Semi-empirical from Ψ-scans
Max. and min. transmission	1.000 and 0.6264	0.9991 and 0.9761
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data/restraints/parameters	3492/0/281	2218/0/183
Goodness-of-fit on F^2	1.143	1.135
Final R indices ($I>2\sigma(I)$)	$R_1=0.0324$, $wR_2=0.0770$	$R_1=0.0405$, $wR_2=0.0982$
R indices (all data)	$R_1=0.0429$, $wR_2=0.0837$	$R_1=0.0573$, $wR_2=0.1093$
Largest difference peak and hole	0.875 and -1.069 e Å^{-3}	0.118 and -0.121 e Å^{-3}
Computations IBM PC/ Digital-ALPHA	SHELXS-86 [27]	SHELXS-86 [27]
Refinement	SHELXL-93 [28]	SHELXL-93 [28]

[a] For supplementary material, see Section 5.

(49%) of the carbene **3c**, which was recrystallized from hexane at -30°C (yellow needles).

^{1}H-NMR ($CDCl_3$, 270 MHz): $\delta=3.64$ (t, 2H, $^3J=4.9$ Hz, C$\underline{H}_2$), 3.83 (t, 2H, $^3J=4.9$ Hz, C$\underline{H}_2$), 3.91 (s, 3H, O–C$\underline{H}_3$), 4.00 (t, 2H, $^3J=4.8$ Hz, C$\underline{H}_2$), 4.27 (t, 2H, $^3J=4.8$ Hz, C$\underline{H}_2$). ^{13}C-NMR ($CDCl_3$): $\delta=52.1$ (O–$\underline{C}H_3$), 57.8 ($\underline{C}H_2$), 57.9 ($\underline{C}H_2$), 67.3 ($\underline{C}H_2$), 67.5 ($\underline{C}H_2$), 170.7 (C=O_{ester}), 196.9 (C=O_{cis}), 202.2 (C=O_{trans}), 239.2 (C=Cr). IR (KBr cm^{-1}): 2069.7 (s), 1980.6 (m), 1926.1 (vs) [ν(C≡O)], 1713.8 (m) [ν(C=O)]. $C_{12}H_{11}NO_8W$ (481.07) Calc.: C 29.96, H 2.30, N 2.91; Found: C 29.96, H 2.33, N 2.89%.

4.2. General procedure for the synthesis of complexes *6a–c* and isoindole *7*

To a 0.1 M solution of the dehydro amino acid **5** in the solvent indicated one equivalent of the appropriate Fischer carbene **2a–c** is added under argon, and the solution is heated (for the corresponding temperature see Scheme 2) in an ace® pressure tube until TLC (silica gel, 3:1 hexane–ethyl acetate) shows the consumption of **5**. The solvent is removed at reduced pressure and the crude reaction mixture is chromatographed on silica gel with 4:1 hexane–ethyl acetate. The red, first eluted fraction contains the starting carbene complex and α-methoxystyrene, the orange, second one contains the amino acid metal carbenes **6a–c** followed by a strongly fluorescent fraction, which contains the isoindole **7**.

4.2.1. Pentacarbonyl[(ethoxycarbonyl)(N-diphenylmethylenamino)methylene]chromium(0) (6a)

To 419 mg (1.50 mmol) of **5** in 15 ml of toluene 468 mg (1.50 mmol) of pentacarbonyl(methoxyphenylmethylene)chromium(0) **2a** are added and the mixture is heated to 80°C under argon for 5 h. Column chromatography (4:1 hexane–ethyl acetate) yields 336 mg (49%) of the carbene **6a**, which was recrystallized from hexane at $+4$°C (red plates).

^{1}H-NMR ($CDCl_3$, 400 MHz): $\delta=1.41$ (t, 3H, $CH_2C\underline{H}_3$), 4.38 (q, 2H, O–C$\underline{H}_2$), 7.52–7.66 (m, 10H, Ph). ^{13}C-NMR ($CDCl_3$): $\delta=14.3$ ($\underline{C}H_3$), 63.2 ($\underline{C}H_2$), 129.3 (C_{ar}), 129.4 (C_{ar}), 129.9 (C_{ar}), 132.1 (C_{ar}), 165.6 ($\underline{C}$=N), 201.7 (C=Cr), n.o.(C=O_{ester}), 216.2 (C=O_{cis}), 223.2 (C=O_{trans}). IR (KBr cm^{-1}): 2060.3 (s), 1983.1 (m), 1931.2 (vs) [ν(C≡O)], 1720.0 (m) [ν(C=O)]. $C_{22}H_{15}CrNO_7$ (457.36) Calc.: C 57.78, H 3.31, N 3.06; Found: C 57.88, H 3.36, N 2.99%.

Table 2
Selected bond lenghts (Å) and bond angles (°) for **6a**

Bond lengths (Å)			
W(1)–C(1)	2.017(7)	O(2)–C(2)	1.135(8)
W(1)–C(4)	2.023(7)	O(3)–C(3)	1.119(8)
W(1)–C(5)	2.036(7)	O(4)–C(4)	1.153(8)
W(1)–C(2)	2.036(7)	O(5)–C(5)	1.118(8)
W(1)–C(3)	2.050(7)	N(1)–C(6)	1.253(7)
W(1)–C(6)	2.208(6)	N(1)–C(7)	1.283(7)
O(1)–C(1)	1.120(8)	C(6)–C(20)	1.507(8)
Bond angles (°)			
C(1)–W(1)–C(4)	92.0(3)	C(6)–N(1)–C(7)	167.3(6)
C(1)–W(1)–C(5)	90.7(3)	O(1)–C(1)–W(1)	179.7(6)
C(1)–W(1)–C(2)	89.2(3)	O(3)–C(3)–W(1)	176.8(7)
C(1)–W(1)–C(6)	178.4(3)	N(1)–C(6)–C(20)	113.2(5)
C(1)–W(1)–C(3)	89.7(3)	N(1)–C(6)–W(1)	125.4(4)
C(4)–W(1)–C(6)	88.8(2)	C(20)–C(6)–W(1)	121.3(4)
C(5)–W(1)–C(6)	87.9(3)	N(1)–C(7)–C(8)	119.1(5)

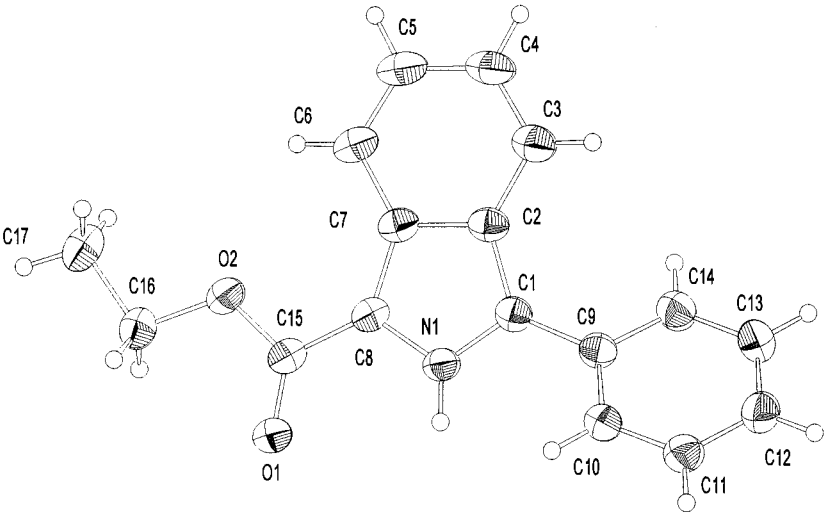


Fig. 2. ORTEP projection of isoindole **7** with the atom numbering scheme.

*4.2.2. Pentacarbonyl[(ethoxycarbonyl)(N-diphenylmethylenamino)methylene]molybdenum(0) (**6b**)*

To 419 mg (1.50 mmol) of **5** in 15 ml of THF 534 mg (1.50 mmol) of pentacarbonyl(methoxyphenylmethylene)molybdenum(0) **2b** are added and the mixture is heated to 66°C under argon for 4 h. Column chromatography (4:1 hexane–ethyl acetate) yields 158 mg (21%) of the carbene **6b**, which was recrystallized twice from hexane–benzene at −30°C (orange plates).

^{1}H-NMR ($CDCl_3$, 400 MHz): $\delta = 1.41$ (t, 3H, $CH_2C\underline{H}_3$), 4.38 (q, 2H, O–$C\underline{H}_2$), 7.53–7.67 (m, 10H, Ph). ^{13}C-NMR ($CDCl_3$): $\delta = 14.2$ ($\underline{C}H_3$), 63.1 ($\underline{C}H_2$), 129.2 (C_{ar}), 129.3 (C_{ar}), 129.8 (C_{ar}), 132.1 (C_{ar}), 165.5 ($\underline{C}$=N), 197.4 (C=Mo), n.o. (C=O_{ester}), 216.1 (C=O_{cis}), 223.1 (C=O_{trans}). IR (CH_2Cl_2 cm^{-1}): 2062.4 (s), 1940.0 (vs) [ν(C≡O)], 1721.0 (w) [ν(C=O)]. $C_{22}H_{15}MoNO_7 \cdot C_6H_6$ (579.41) Calc.: C 58.04, H 3.66, N 2.42; Found: C 57.56, H 3.52, N 2.79%.

*4.2.3. Pentacarbonyl[(ethoxycarbonyl)(N-diphenylmethylenamino)methylene]tungsten(0) (**6c**)*

To 419 mg (1.50 mmol) of **5** in 15 ml of THF 666 mg (1.50 mmol) of pentacarbonyl(methoxyphenylmethylene)tungsten(0) **2c** are added and the mixture is heated to 66°C under argon for 18 h. Column chromatography (4:1 hexane–ethyl acetate) yields 239 mg (27%) of the carbene **6c**, which was recrystallized from hexane at +4°C (orange plates).

^{1}H-NMR ($CDCl_3$, 270 MHz): $\delta = 1.39$ (t, 3H, $CH_2C\underline{H}_3$), 4.38 (q, 2H, O–$C\underline{H}_2$), 7.51–7.67 (m, 10H, Ph). ^{13}C-NMR ($CDCl_3$): $\delta = 14.2$ ($\underline{C}H_3$), 63.3 ($\underline{C}H_2$), 128.9 (C_{ar}), 129.4 (C_{ar}), 129.9 (C_{ar}), 132.2 (C_{ar}), 166.1 (C=N), 183.3 (C=W), n.o.(C=O_{ester}), 197.4 (C=O_{cis}), 202.7 (C=O_{trans}). IR (KBr cm^{-1}): 2066.8 (s), 1975.9 (m), 1925.4 (vs) [ν(C≡O)], 1720.3 (m) [ν(C=O)]. $C_{22}H_{15}NO_7W$ (589.21) Calc.: C 44.85, H 2.57, N 2.38; Found: C 44.76, H 2.52, N 2.32%.

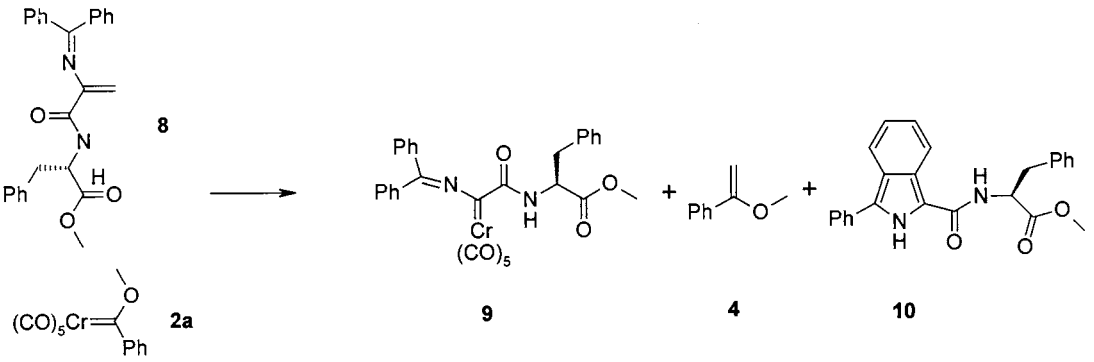
*4.2.4. 3-Phenylisoindole-1-carboxylicacid ethylester (**7**)*

As an example the isolation of **7** is described for the reaction yielding **6a**. After chromatographic separation (4:1 hexane–ethyl acetate) of **6a** a strongly fluorescent fraction is collected, which contains impure **7**. A second column chromatography with 7:3 chloroform–hexane as eluent yields 92 mg (23%) of **7**. Slow crystallization from chloroform–hexane gives analytically pure light yellow crystals of **7**.

^{1}H-NMR ($CDCl_3$, 300 MHz): $\delta = 1.43$ (t, 3H, $CH_2C\underline{H}_3$), 4.39 (q, 2H, O–$C\underline{H}_2$), 7.17 (t, 1H, $^3J = 7.5$ Hz, H_{ar}), 7.32 (t, 1H, $^3J = 7.5$ Hz, H_{ar}), 7.40 (t, 1H, $^3J = 7.1$ Hz, *p*-$H_{arom.}$), 7.51 (t, 2H, $^3J = 7.8$ Hz, *m*-$H_{arom.}$), 7.78 (d, 2H, $^3J = 7.8$ Hz, *o*-$H_{arom.}$), 7.95 (d, 1H, $^3J = 8.2$ Hz, H_{ar}), 8.12 (d, 1H, $^3J = 8.2$ Hz, H_{ar}), 11.15 (s, broad, 1H, NH). ^{13}C-NMR ($CDCl_3$): $\delta = 14.7$ ($\underline{C}H_3$), 60.3 ($\underline{C}H_2$), 111.6 (C_{ar}), 120.8 (C_{ar}), 120.9 (C_{ar}), 122.9 (C_{ar}), 123.2 (C_{ar}), 125.8 (C_{ar}), 127.3 (C_{ar}), 128.0 (C_{ar}), 128.3 (C_{ar}), 129.0 (C_{ar}), 129.2 (C_{ar}), 131.5 (C_{ar}), 162.5 (C=O_{ester}). IR (CH_2Cl_2 cm^{-1}): 3686.0 (m), 2944.0

Table 3
Selected bond lenghts (Å) and bond angles (°) for **7**

Bond lengths (Å)			
N(1)–C(1)	1.353(2)	C(3)–C(4)	1.356(3)
N(1)–C(8)	1.371(2)	C(4)–C(5)	1.407(3)
C(1)–C(2)	1.413(2)	C(5)–C(6)	1.355(3)
C(1)–C(9)	1.465(2)	C(6)–C(7)	1.417(2)
C(2)–C(3)	1.418(2)	C(7)–C(8)	1.406(2)
C(2)–C(7)	1.423(2)	C(8)–C(15)	1.436(2)
Bond angles (°)			
C(1)–N(1)–C(8)	112.24(13)	C(3)–C(2)–C(7)	119.8(2)
N(1)–C(1)–C(2)	106.49(14)	C(4)–C(3)–C(2)	118.5(2)
N(1)–C(1)–C(9)	123.65(14)	C(3)–C(4)–C(5)	121.6(2)
C(2)–C(1)–C(9)	129.8(2)	N(1)–C(8)–C(15)	120.73(14)
C(1)–C(2)–C(3)	132.6(2)	C(7)–C(8)–C(15)	132.6(2)
C(1)–C(2)–C(7)	107.55(14)	O(1)–C(15)–C(8)	125.3(2)



Scheme 4.

(vs), 2401.2 (s), 1736.3 (m), 1718.1 (m), 1521.1 (s), 1466.7 (vs). MS (EI) m/z (%) = 265.3 (100); MS (ESI) m/z (%) = 287.2 (100), 265.2 (24), 219.2 (10), 191.2 (20). UV ($CHCl_3$): λ_{max} = 369.4 nm. $C_{17}H_{15}NO_2$ (265.31) Calc.: C 76.96, H 5.69, N 5.28; Found: C 76.34, H 5.75, N 5.11%.

Alternatively, **7** can be synthesized by stirring 100 mg (0.22 mmol) of **6a** and 65 mg (0.22 mmol) Na_2PdCl_4 in 7 ml of methanol for 1 h. The mixture is filtered on Celite by suction to remove the precipitated palladium and evaporated in vacuo. Column chromatography with 7:3 chloroform–hexane as eluent yields 50 mg (87%) of pure **7**, identified by its ^{1}H-NMR and mass spectra.

4.3. *N*-Diphenylmethylene-α,β-didehydroalanyl-(L)-phenylalanine methylester (*8*)

To 160 mg (0.4 mmol) of *N*-diphenylmethylene-(L)-seryl-(L)-phenylalanine methylester in 10 ml of dry CH_2Cl_2, 124 μl (0.8 mmol) of 1,3-diisopropylcarbodiimide and 12 mg (0.4 mmol) of CuCl are added. The mixture is stirred for 32 h at 40°C with exclusion of moisture and light, filtered on Celite by suction, washed with H_2O (3 × 10 ml), dried (Na_2SO_4) and evaporated in vacuo. Column chromatography (silica gel; 4:1 hexane–ethyl acetate) is used to obtain 134 mg (81%) of pure compound **8** as a foam.

^{1}H-NMR (CD_2Cl_2, 300 MHz): δ = 3.04 (m, 2H, C$\underline{H}_2$), 3.63 (s, 3H, O–C$\underline{H}_3$), 4.12 (s, 1H, =C$\underline{H}_2$), 4.78 (dd, 1H, α-$\underline{H}$), 5.20 (s, 1H, =C$\underline{H}_2$), 6.85 (d, 1H, N$\underline{H}$), 6.91–7.59 (m, 15H, $H_{arom.}$). ^{13}C-NMR (CD_2Cl_2): δ = 36.7 ($\underline{C}H_2$), 51.2 (O$\underline{C}H_3$), 60.1 (α-$\underline{C}$), 104.3 (C), 125.6 (C), 126.0 (C), 127.3 (C), 127.4 (C), 127.6 (C), 127.9 (C), 128.2 (C), 128.4 (C), 130.3 (C), 134.1 (C), 135.2 (C), 137.6 (C), 147.2 (C), 165.6 (C=N), 169.4 ($C{=}O_{amide}$), 170.8 ($C{=}O_{ester}$). IR (CH_2Cl_2 cm^{-1}): 1746.0 (s), 1679.2 (vs), 1625.0 (s), 1598.1 (s), 1553.0 (vs). $C_{26}H_{24}N_2O_3$ (412.48). MS (FAB): m/z = 413 (68) [M + H$^+$], 435 (13) [M + Na$^+$], 825 (55) [2M + H$^+$].

4.4. Peptide chromium carbene (*9*)

To 79 mg (0.19 mmol) of **8** in 15 ml of toluene 60 mg (0.19 mmol) of pentacarbonyl(methoxyphenylmethylene)chromium(0) **2a** are added and the mixture is heated to 80°C under argon for 4 h. Repeated column chromatography (3:1 hexane–ethyl acetate) yields 26 mg (23%) of the carbene complex **9** (orange powder).

^{1}H-NMR (CD_2Cl_2, 300 MHz): δ = 3.35 (s, 3H, O–C$\underline{H}_3$), 3.72 (m, 2H, C$\underline{H}_2$), 4.17 (m, 1H, α-$\underline{H}$), 6.78 (d, 1H, N$\underline{H}$), 7.22–7.53 (m, 15H, $H_{arom.}$). ^{13}C-NMR (CD_2Cl_2): δ = 36.0 ($\underline{C}H_2$), 51.0 (O$\underline{C}H_3$), 60.0 (α-$\underline{C}$), 125.2 (C), 126.4 (C), 127.9 (C), 128.1 (C), 128.8 (C), 129.5 (C), 129.8 (C), 130.2 (C), 130.5 (C), 134.3 (C), 135.5 (C), 137.5 (C), 145.3 (C), 162.5 (C=N), 170.8 ($C{=}O_{amide}$), 172.4 ($C{=}O_{ester}$), 202.0 (C=Cr), 217.8 ($C{=}O_{cis}$), 224.7 ($C{=}O_{trans}$). IR (CH_2Cl_2 cm^{-1}): 2061.1 (s), 1941.3 (vs), 1751.1 (s), 1712.4 (vs). $C_{30}H_{22}CrN_2O_8$ (590.51). MS (FAB): m/z = 591 [M + H$^+$], 562 [M − CO], 536 [M − 2CO].

5. Supplementary material

Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 118820 (**6c**) and CCDC 118819 (**7**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk].

Acknowledgements

We thank Deutsche Forschungsgemeinschaft, Fonds der Chemischen Industrie and Wacker Chemie, München, for generous support and Professor W.

Steglich and Dr W. Spahl, Munich, for the mass spectra.

References

[1] T. Ederer, K. Polborn, W. Beck, Z. Anorg. Allg. Chem. (in press).
[2] K. Severin, R. Bergs, W. Beck, Angew. Chem. 110 (1998) 1722; Angew. Chem. Int. Ed. Engl. 37 (1998) 1634.
[3] (a) D. Mani, H.-T. Schacht, A.K. Pawell, H. Vahrenkamp, Organometallics 6 (1987) 1360. (b) D. Mani, H.-T. Schacht, A.K. Powell, H. Vahrenkamp, Chem. Ber. 122 (1989) 2245. (c) B. Kayser, H. Nöth, M. Schmidt, W. Steglich, W. Beck, Chem. Ber. 129 (1996) 1617. (d) J.A. Wiles, S.H. Bergens, J. Am. Chem. Soc. 119 (1997) 2940. (e) B. Kayser, C. Missling, J. Knizek, H. Nöth, W. Beck, Eur. J. Inorg. Chem. (1998) 375.
[4] (a) G. Jaouen, A. Vessiéres, I.S. Butler, Acc. Chem. Res. 26 (1993) 361. (b) A. Varenne, A. Vessiéres, M. Salmain, S. Durand, P. Brossier, G. Jaouen, Anal. Biochem. 242 (1996) 172. (c) A.J. Gleichmann, J.M. Wolff, W.S. Sheldrick, J. Chem. Soc. Dalton Trans. (1995) 1549. (d) J.M. Wolff, A.J. Gleichmann, W.S. Sheldrick, J. Inorg. Biochem. 59 (1995) 219. (e) J.M. Wolff, W.S. Sheldrick, Chem. Ber. 130 (1997) 981. (f) J. Organomet. Chem. 531 (1997) 141. (g) M. Schweiger, T. Ederer, K. Sünkel, W. Beck, J. Organomet. Chem. 545 (1997) 17.
[5] J. Halpern, Pure Appl. Chem. 55 (1983) 99.
[6] For recent reviews see: (a) K.H. Dötz, Angew. Chem. Int. Ed. Engl. 23 (1984) 587. (b) W.D. Wulff, in: E.W. Abel, F.G. Stone, G. Wilkinson (Eds.), Comprehensive Organometallic Chemistry II, vol. 12, Pergamon, Oxford, 1995, p. 470. (c) L.S. Hegedus, Tetrahedron 53 (1997) 4105. (d) W.D. Wulff, Organometallics 17 (1998) 3116. (e) K.H. Dötz, J. Pfeiffer, Transition Met. Org. Synth. 1 (1998) 335. (f) J.W. Herndon, Coord. Chem. Rev. 181 (1999) 177.
[7] (a) L.S. Hegedus, Acc. Chem. Res. 28 (1995) 299. (b) W.C. Haase, M. Nieger, K.H. Dötz, Chem. Eur. J. 5 (1999) 2014.
[8] K.H. Dötz, R. Ehlenz, Chem. Eur. J. 3 (1997) 1751.
[9] D. Dvorák, M. Ludwig, Organometallics 17 (1998) 3627.
[10] (a) R. Imwinkelried, L.S. Hegedus, Organometallics 7 (1988) 702. (b) M.A. Schwindt, T. Lejon, L.S. Hegedus, Organometallics 9 (1990) 2814.
[11] (a) K.H. Dötz, W.C. Haase, M. Klumpe, M. Nieger, Chem. Commun. (Cambridge) (1997) 1217. (b) J. Barluenga, F. Aznar, S. Barluenga, M. Fernandez, A. Martin, S. Garcia-Granda, A. Pinery-Nicolas, Chem. Eur. J. 4 (1998) 2280. (c) E.O. Fischer, K.H. Dötz, Chem. Ber. 105 (1972) 3966.
[12] U. Schmidt, A. Lieberknecht, J. Wild, Synthesis (1988) 159.
[13] G. Jung, Angew. Chem. 103 (1991) 1067.
[14] K. Morimoto, N. Shimada, H. Naganawa, T. Takita, H. Umezawa, J. Antibiot. 34 (1981) 1613.
[15] T. Shiroza, N. Ebisawa, A. Kojima, K. Furihata, T. Endo, H. Seto, N. Otake, Agric. Biol. Chem. 46 (1982) 1885.
[16] R.J. Stonard, R.J. Andersen, J. Org. Chem. 45 (1980) 3687.
[17] Z. Arnold, Synthesis (1990) 39.
[18] (a) E.O. Fischer, F.R. Kreißl, in: W.A. Herrmann (Ed.), Synthetic Methods of Organometallic and Inorganic Chemistry, vol. 7, Thieme, Stuttgart, 1997, p. 129. (b) S.U. Tumer, J.W. Herndon, L.A. McMullen, J. Am. Chem. Soc. 114 (1992) 8394.
[19] C. Balsamini, E. Duranti, L. Mariani, A. Salvatori, G. Spadoni, Synthesis (1990) 779.
[20] G. Tarzia, C. Balsamini, G. Spadoni, E. Duranti, Synthesis (1988) 515.
[21] G. Wulff, H. Böhnke, H.T. Klinken, Liebigs Ann. Chem. (1988) 501.
[22] U. Schubert, Transition Metal Carbene Complexes, Verlag Chemie, Weinheim, 1983.
[23] A. Pawda, R.J. Rosenthal, W. Dent, P. Filho, N.J. Turro, D.A. Hrovat, I.R. Gould, J. Org. Chem. 49 (1984) 3174.
[24] R.I. Fryer, J.V. Earley, L.H. Sternbach, J. Org. Chem. 34 (1969) 649.
[25] Hoffmann-La Roche Inc., Nutley, NJ, US Patent Appl. No. 789 905.
[26] M.J. O'Donnell, R.L. Polt, J. Org. Chem. 47 (1982) 2663.
[27] G.M. Sheldrick, SHELXS-86, Program for Crystal Structure Solution, University of Göttingen, Germany, 1986.
[28] G.M. Sheldrick, SHELXL-93, Program for Crystal Structure Refinement, University of Göttingen, Germany, 1993.