ELSEVIER

Journal of Organometallic Chemistry 531 (1997) 141–149

Journal of Organometallic Chemistry

Bis(arene) ruthenium(II) complexes containing η^6-coordinated phenylalanine derivatives

J.M. Wolff, W.S. Sheldrick *

Lehrstuhl für Analytische Chemie, Ruhr-Universität Bochum, D-44780 Bochum, Germany

Received 8 July 1996

Abstract

Bis(arene) ruthenium(II) complexes of the type $[Ru(\eta^6\text{-aa})(\eta^6\text{-cymene})][CF_3SO_3]_n$ **2–5**, containing the phenylalanine (HpheOH) derivatives, N-acetyl-L-phenylalanine methyl ester (**2**), L-phenylalaninium methyl ester $[H_2pheOMe]^+$ (**3**), N-acetyl-L-phenylalanine (**4**) and HpheOH (**5**), were prepared by treatment of $[Ru\{(CH_3)_2CO\}_3(\eta^6\text{-cymene})]^{2+}$ with the appropriate derivative (aa) in CH_2Cl_2 (**2**, **3**) or CF_3COOH (**4**, **5**). Whereas **2**, **4** and **5** all contain dications ($n = 2$), utilisation of the protonated amino acid $[H_2pheOMe]^+$ was necessary in CH_2Cl_2 to prevent κN coordination of the unprotected NH_2 group in this methyl ester, leading thereby to the formation of a triply charged sandwich cation $[Ru(\eta^6\text{-cymene})(\eta^6\text{-}H_2pheOMe)]^{3+}$ in **3** ($n = 3$). The feasibility of $(\eta^6\text{-cymene})Ru^{II}$ labelling for peptides with aromatic side chains was demonstrated by the synthesis of the complex $[\{Ru(\eta^6\text{-cymene})\}_2\{cyclo\text{-(phephe)}\}][CF_3SO_3]_4$ **6**. Crystal structures are presented for the compounds **2**, **3** and **6**.

Keywords: Bis(arene) ruthenium(II); Bioorganometallic chemistry; Amino acid; Phenylalanine; Dipeptide; Crystal structure

1. Introduction

The perspectives of bioorganometallic chemistry in the development of immunoassay procedures [1,2] and the analysis and molecular recognition of enzyme active sites have been discussed in a recent review article by Jaouen et al. [3]. Despite the apparent potential of organometallic labelling, surprisingly few examples of η^6-coordination of transition metals by the aromatic side chains of the amino acids phenylalanine (L-HpheOH), tyrosine (L-HtyrOH) and tryptophan (L-HtrpOH) have been reported. These appear to be restricted to $CpRu^{II}$ and Cp^*Ru^{II} ($Cp^* = C_5Me_5$) sandwich complexes.

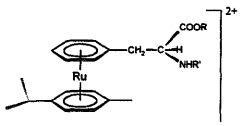
The facile preparation of η^6-coordinated $CpRu^{II}$ complexes of the ethyl esters of N-acetyl-L-phenylalanine, N-acetyl-L-tyrosine and N-acetyl-L-tryptophan was reported by Moriarty et al. in 1987 [4]. More recently, the groups of Pearson [5] and Rich [6] have demonstrated that the diaryl coupling, required for the total synthesis of cyclic diphenyl ether peptides such as the protease inhibitor K-13, may be achieved under very mild conditions by activation of protected p-Cl-phenylalanine through η^6-coordination of the $CpRu^{II}$ fragment. We have employed $[(RuCp^*Cl)_2(\mu\text{-}Cl)_2]$ and $[RuCp^*(MeCN)_3]^+$ for the first direct preparation of η^6-coordinated complexes of the free amino acids L-HpheOH, L-HtyrOH and L-HtrpOH [7,8]. Reaction of $[RuCp^*(MeCN)_3]^+$ with dipeptides such as HphepheOH, HtrptrpOH, HtrppheOH or HphetrpOH in a 2:1 molar ratio delivers complexes with two organometallic sandwich centres as labelling sites [8,9]. Interestingly, only indole-coordinated 1:1 complexes can be isolated for the latter two mixed dipeptides by size-exclusion chromatography, indicating a chemospecificity for this partially localised arene π system over the highly delocalised phenyl entity. The feasibility of peptide synthesis from individual Cp^*Ru^{II} labelled amino acids was demonstrated by the preparation of $[RuCp^*\{\eta^6\text{-}cyclo\text{-}(phephe)\}]^+$ using $[(RuCp^*(\eta^6\text{-L-HpheOMe})]^+$ [8].

We now present the first examples of organometallic labelling of an aromatic amino acid (HpheOH) and its derivatives with an $(\eta^6\text{-arene})Ru^{II}$ fragment. Cationic $bis(\eta^6\text{-arene})Ru^{II}$ sandwich complexes of the protected phenylalanine derivatives, AcpheOMe (N-acetyl-L-phenylalanine methyl ester), $[H_2pheOMe]^+$ (L-phenylalaninium methyl ester) and *cyclo*-(phephe) can be obtained by treatment of $[Ru(acetone)_3(\eta^6\text{-cymene})]^{2+}$ (**1**) with the chosen compounds in CH_2Cl_2 (cymene = 4-

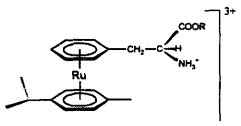
* Corresponding author.

0022-328X/97/$17.00 Published by Elsevier Science S.A.
PII S0022-328X(96)06708-3

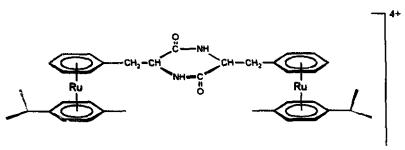
methylisopropylbenzene) [10–12]. The entropically favoured sandwich complexes can also be prepared for HpheOH itself and AcpheOH (N-acetyl-L-phenylalanine) by performing the reaction in trifluoroacetic acid.



Cations of **2** (R = Me, R' = Ac), **4** (R = H, R' = Ac)



Cation of **3**



Cation of **6**

2. Experimental details

Solvents were dried and distilled before use. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX 400 spectrometer, IR spectra as KBr disks on a Perkin–Elmer 1760 spectrometer and FAB mass spectra on a VG Autospec instrument employing 3-nitrobenzyl alcohol as the matrix. Elemental analyses were performed by Beller, Göttingen. The starting compound $[Ru(acetone)_3(\eta^6\text{-cymene})][CF_3SO_3]_2$ (**1**) was prepared from $RuCl_3 \cdot xH_2O$ (Heräus, Karlsruhe) by abstracting the chloride ions of the intermediate product $[\{RuCl(\eta^6\text{-cymene})\}_2(\mu\text{-}Cl)_2]$ [13] with $Ag(CF_3SO_3)$ in acetone [10,11]. Phenylalanine and its derivatives were purchased from Bachem (Heidelberg) and Calbiochem-Novabiochem (Bad Soden) and used as received. All reactions were carried out under argon by use of standard Schlenk techniques.

2.1. Preparation of complexes 2–6

2.1.1. $[Ru(\eta^6\text{-AcpheOMe})(\eta^6\text{-cymene})][CF_3SO_3]_2$ (2)

AcpheOMe (89 mg, 0.4 mmol) was added to a solution of **1** (284 mg, 0.4 mmol) in 10 ml CH_2Cl_2 and stirred for 4 h at reflux. The resulting precipitate was washed with CH_2Cl_2 and diethyl ether and dried in vacuum to afford **2** (yield 87%). Light-brown crystals of the compound may be obtained by covering a methanol solution of **2** with diethyl ether and leaving to stand. Anal. Found: C, 38.6; H, 3.7; N, 1.9; $M = 754.7$. $C_{24}H_{29}NO_9F_6S_2Ru$ Calc.: C, 38.2; H, 3.9; N, 1.9%. FAB mass spectrum: m/z 606 (13%) $[M - CF_3SO_3]^+$, 456 (100%) $[M - 2CF_3SO_3]^+$, 323 (33%) $[M - 2CF_3SO_3 - \text{cymene}]^+$. ^{1}H NMR (CD_3NO_2): δ 1.47 (d, 6H, cymene), 2.01 (s, 3H, Ac), 2.68 (s, 3H, cymene), 3.17 (sp, 1H, cymene), 3.21 (dd, 1H, β-H), 3.41 (dd, 1H, β-H), 3.85 (s, 3H, OCH_3), 4.85 (dd, 1H, α-H), 7.12 (m, 9H, cymene + Ph), 7.22 (d, NH). ^{13}C NMR (CD_3NO_2): δ 19.9 (cymene), 22.7 (Ac), 22.9, 33.4 (cymene), 36.9 (β-*C*), 53.8 (*OC*H_3), 53.9 (α-*C*), 93.8, 95.2, 95.9, 96.2, 96.7, 96.8 (cymene + Ph), 113.8, 115.1 (cymene), 122.3 (q, *C*$F_3SO_3^-$), 124.5 (Ph), 171.6 (*C*OO), 172.4 (NH*C*O). IR: ν(NH) 3069s; ν(CO) 1736s, 1669s; ν(NH) 1541m cm^{-1}.

2.1.2. $[Ru(\eta^6\text{-cymene})(\eta^6\text{-}H_2\text{pheOMe})][CF_3SO_3]_3$ (3)

A solution of HpheOMe · HCl (86 mg, 0.4 mmol) in 5 ml CH_3OH was stirred with $Ag(CF_3SO_3)$ (104 mg, 0.4 mmol) for 10 min and the precipitated AgCl filtered off. After washing with CH_3OH the solvent was removed and a solution of **1** (284 mg, 0.4 mmol) in CH_2Cl_2 added to the resulting solid. The suspension was then refluxed for 48 h. The off-white precipitate was washed with CH_2Cl_2 and dried in vacuum to deliver **3** (yield 79%). White crystals for X-ray analysis were grown by covering an acetonitrile solution of **3** with diethyl ether and leaving to stand. Anal. Found: C, 32.7; H, 3.1; N, 1.7; $M = 862.7$. $C_{23}H_{28}NO_{11}F_9S_3Ru$ Calc.: C, 32.0; H, 3.3; N, 1.6%. FAB mass spectrum: m/z 714 (16%) $[M - CF_3SO_3]^+$, 564 (45%) $[M - 2CF_3SO_3]^+$, 414 (100%) $[M - 3CF_3SO_3]^+$. ^{1}H NMR (CD_3NO_2): δ 1.50 (d, 6H, cymene), 2.71 (s, 3H, cymene), 3.23 (sp, 1H, cymene), 3.68 (dd, 1H, β-H), 3.89 (dd, 1H, β-H), 3.93 (s, 3H, OCH_3), 4.69 (m, 1H, α-H), 7.13 (m, 7H, cymene + Ph), 7.23 (d, 1H, cymene), 7.40 (d, 1H, cymene), 8.04 (br s, NH_3^+). ^{13}C NMR (CD_3NO_2): δ 19.9, 22.8, 23.0, 33.4 (cymene), 34.3

(β-*C*), 54.7 (OCH_3), 55.0 (α-*C*), 94.1, 94.2, 95.6, 95.7, 96.2, 96.5, 96.6, 96.8, 97.8 (cymene + Ph), 111.1, 115.7 (cymene), 121.9 (q, *C*$F_3SO_3^-$), 125.0 (Ph), 168.4 (*C*OO). IR: ν(NH) 3078s; ν(CO) 1769s; δ(NH) 1607m, 1536m cm^{-1}.

2.1.3. *[Ru(η⁶-AcpheOH)(η⁶-cymene)][CF_3SO_3]$_2$ (4)*

AcpheOH (83 mg, 0.4 mmol) was added to a solution of **1** (284 mg, 0.4 mmol) in 6 ml CF_3COOH, which was then stirred for 8 h at 50 °C. Slow addition of 15 ml diethyl ether to the resulting solution at 0 °C provided an off-white precipitate which was washed and dried in vacuum to afford **4** (yield 80%). Anal. Found: C, 35.2; H, 3.8; N, 1.8; $M = 740.7$. $C_{23}H_{27}NO_9F_6S_2Ru$ Calc.: C, 37.3; H, 3.7; N 1.9%. FAB mass spectrum: *m/z* 592 (7%) $[M - CF_3SO_3]^+$, 442 (100%) $[M - 2CF_3SO_3]^+$. ^1H NMR (CD_3NO_2): δ 1.48 (d, 6H, cymene), 2.08 (s, 3H, Ac), 2.69 (s, 3H, cymene), 3.17 (sp, 1H, cymene), 3.25 (dd, 1H, β-H, 3.46 (dd, 1H, β-H), 4.86 (dd, 1H, α-H), 7.11 (m, 7H, cymene + Ph), 7.21 (d, 1H, cymene), 7.33 (d, NH), 7.37 (d, 1H, cymene). ^{13}C NMR (CD_3NO_2): δ 19.9 (cymene), 22.7 (Ac), 22.9, 33.4 (cymene), 36.8 (β-*C*), 54.1 (α-*C*), 94.0, 95.2, 95.5, 96.4, 96.5, 96.7, 97.0 (cymene + Ph), 113.3, 115.1 (cymene), 122.1 (q, *C*$F_3SO_3^-$), 124.4 (Ph), 171.9 (*C*OO), 173.5 (NH*C*O). IR: ν(NH) 3077s; ν(COO) 1739s; ν(NHCO) 1671s; δ(NH) 1535m cm^{-1}.

2.1.4. *[Ru(η⁶-cymene)(η⁶-HpheOH)][CF_3SO_3]$_2$ (5)*

1 (284 mg, 0.4 mmol) and HpheOH (6 mg, 0.4 mmol) were heated together with stirring for 12 h at 50 °C in 6 ml CF_3COOH. After cooling the resulting solution, slow addition of 15 ml diethyl ether afforded a yellowish precipitate, which was washed and dried in vacuum to provide **5** (yield 83%). **1** was also obtained by base-catalysed ester cleavage of **3** (86 mg, 0.1 mmol) in aqueous solution (5 ml). After raising the pH to ca. 12 with 0.1 M NaOH and stirring for 15 min, the pH was lowered to the original value (5.6) by addition of a CF_3SO_3H solution. The volume was reduced to ca. 2 ml and **1** separated from Na(CF_3SO_3) by size-exclusion chromatography with water as eluent and Sephadex LH-20 as stationary phase (yield 53%). Anal. Found: C, 32.5; H, 3.4; N, 1.7; $M = 689.6$. $C_{21}H_{25}NO_8F_6S_2Ru \cdot CF_3COOH$ Calc.: C, 34.0; H, 3.2; N, 1.7%. FAB mass spectrum: *m/z* 550 (13%) $[M - CF_3SO_3]^+$, 533 (21%) $[M - NH_3]^+$, 400 (100%) $[M - 2CF_3SO_3]^+$. ^1H NMR (CD_3NO_2): δ 1.48 (d, 6H, cymene), 2.70 (s, 3H, cymene), 3.20 (sp, 1H, cymene), 3.64 (dd, 1H, β-H), 3.72 (dd, β-H), 4.64 (dd, 1H, α-H), 7.13 (m, 7H, cymene + Ph), 7.25 (d, NH_2), 7.32 (d, 1H, cymene), 7.39 (d, 1H, cymene). ^{13}C NMR (CD_3NO_2): δ 19.9, 22.9, 33.4 (cymene), 34.8 (β-*C*), 54.8 (β-*C*), 94.0, 95.5, 95.8, 96.1, 96.4, 96.8, 98.0 (cymene + Ph), 111.5, 115.6 (cymene), 121.9 (q, *C*$F_3SO_3^-$), 124.9 (Ph), 169.9 (*C*OO). IR: ν(NH) 3078s; ν(COO) 1746s, 1677m; δ(NH) 1534w cm^{-1}.

2.1.5. *[{Ru(η⁶-cymene)}$_2$(cyclo-(phephe))][CF_3SO_3]$_4$ (6)*

Cyclo-(phephe) (59 mg, 0.2 mmol) was added to a solution of **1** (284 mg, 0.4 mmol) in 10 ml CH_2Cl_2 and

Table 1
Crystal and refinement data for **2**, **3** and **6**

	2	**3**	**6**
space group	$P2_12_12_1$	$P2_12_12_1$	$C2$
a (Å)	8.776(2)	10.533(2)	26.640(5)
b (Å)	14.776(3)	12.409(2)	19.136(4)
c (Å)	23.361(5)	26.091(5)	10.026(2)
β (°)	90	90	96.04(3)
volume (Å^3)	3029(1)	3410(1)	5083(2)
Z	4	4	4
M	754.7	862.7	1361.2
F(000)	1528	1736	2736
D_c (g cm^{-3})	1.655	1.680	1.779
radiation	Mo Kα	Mo Kα	Mo Kα
μ (mm^{-1})	0.742	0.746	0.868
crystal size	0.18 × 0.36 × 0.72	0.24 × 0.27 × 0.74	0.27 × 0.28 × 0.58
$2\theta_{max}$ (°)	50	50	50
index ranges	0/10, 0/17, 0/27	0/12, 0/14, 0/31	-31/31, 0/22, 0/11
independent reflections	2943	3405	4567
reflections with $I > 2\sigma(I)$	2218	1813	3809
parameters	361	401	637
goodness of fit S	1.056	1.041	1.077
R_1 ($I > 2\sigma(I)$)	0.051	0.075	0.070
wR_2 (all data)	0.135	0.224	0.235
residual electron density (e Å^{-3})	-0.38/0.49	-0.39/0.64	-1.27/2.41

Table 2
Atomic coordinates [$\cdot 10^4$] and equivalent isotropic temperature factors U_{eq} [$Å^2 \cdot 10^3$]. Equivalent isotropic temperature factors U_{eq} are defined as one third of the trace of the orthogonalized U_{ij} tensors

Atom	x	y	z	U_{eq}
2				
Ru	1493(1)	−26(1)	−1782(1)	37(1)
C(41)	703(6)	−89(5)	−885(3)	49(2)
C(42)	2040(8)	414(4)	−907(3)	49(3)
C(43)	3345(6)	43(4)	−1149(3)	50(2)
C(44)	3313(6)	−830(4)	−1370(3)	44(2)
C(45)	1976(8)	−1333(3)	−1348(3)	50(3)
C(46)	671(6)	−963(4)	−1106(3)	46(3)
C(411)	−685(9)	346(8)	−613(4)	74(4)
C(412)	−2201(12)	−147(11)	−720(6)	93(5)
C(413)	−393(22)	462(18)	31(4)	168(11)
C(441)	4734(10)	−1267(8)	−1614(5)	68(3)
C(31)	57(7)	−307(3)	−2539(3)	41(2)
C(32)	−525(6)	459(4)	−2272(3)	42(2)
C(33)	414(8)	1200(3)	−2171(3)	53(3)
C(34)	1936(8)	1173(4)	−2335(3)	63(3)
C(35)	2517(6)	406(5)	−2602(3)	63(4)
C(36)	1578(8)	−334(4)	−2704(3)	52(3)
C(3)	−958(11)	−1117(5)	−2665(4)	53(3)
C(2)	−1824(11)	−1040(7)	−3239(4)	48(2)
N(2)	−826(12)	−942(6)	−3720(4)	57(3)
O(21)	−1003(12)	−2421(6)	−3993(4)	82(3)
C(21)	−549(13)	−1646(8)	−4080(4)	52(3)
C(22)	387(20)	−1417(9)	−4607(5)	83(5)
C(1)	−2977(12)	−263(7)	−3207(5)	54(3)
O(1)	−3787(10)	−135(7)	−2800(3)	82(3)
O(11)	−3002(11)	266(6)	−3676(4)	80(3)
C(12)	−3992(18)	1022(11)	−3665(7)	104(5)
S(100)	3867(3)	2852(2)	−3126(1)	57(1)
O(110)	3869(11)	−3802(5)	−3268(4)	94(3)
O(120)	5192(11)	−2547(7)	−2816(4)	85(3)
O(130)	2445(11)	−2510(7)	−2920(5)	104(4)
C(100)	4129(16)	−2277(9)	−3803(4)	74(4)
F(110)	3090(13)	−2540(9)	−4179(4)	140(4)
F(120)	4035(13)	−1381(5)	−3757(4)	123(4)
F(130)	5482(11)	−2487(7)	−4025(4)	114(3)
S(200)	3799(4)	8454(2)	1058(1)	67(1)
O(210)	3534(17)	9395(6)	1150(6)	86(4)
O(220)	2720(18)	7767(9)	1202(7)	111(5)
O(230)	5215(16)	8156(15)	1289(8)	148(7)
O(211)	2708(41)	9183(22)	1047(19)	89(7)
O(221)	3563(57)	7633(16)	1370(15)	89(7)
O(231)	5228(28)	8806(30)	1253(18)	89(7)
C(200)	4079(22)	8282(8)	299(4)	155(10
F(210)	4297(24)	7419(8)	177(7)	131(5)
F(220)	2750(22)	8537(15)	80(9)	184(8)
F(230)	5023(22)	8916(13)	119(8)	169(7)
F(211)	3981(37)	8970(15)	−58(10)	72(8)
F(221)	3320(53)	7640(27)	20(18)	123(14)
F(231)	5270(33)	7719(24)	265(16)	99(11)
3				
Ru	2258(1)	8872(1)	1889(1)	65(1)
C(41)	1659(15)	10420(9)	1539(4)	87(6)
C(42)	717(10)	10069(10)	1873(6)	91(6)
C(43)	1013(12)	9842(9)	2381(6)	85(6)
C(44)	2252(15)	9966(9)	2555(3)	85(5)
C(45)	3194(10)	10316(9)	2221(5)	72(5)
C(46)	2898(13)	10543(9)	1713(4)	73(5)
C(411)	1263(37)	10702(18)	995(7)	172(14)
C(412)	331(49)	9953(43)	718(21)	164(24)

Table 2 (continued)

Atom	x	y	z	U_{eq}
3				
C(413)	1349(66)	11934(21)	924(32)	146(15)
C(414)	2193(44)	10429(46)	560(17)	147(19)
C(415)	827(65)	11878(25)	921(34)	146(15)
C(441)	2613(29)	9744(19)	2107(5)	157(11)
C(31)	3630(10)	7868(9)	1461(5)	64(4)
C(32)	2452(13)	7766(10)	1225(4)	90(6)
C(33)	1403(9)	7441(10)	1510(7)	113(9)
C(34)	1533(14)	7219(9)	2029(7)	116(10)
C(35)	2711(18)	7322(10)	2265(4)	109(8)
C(36)	3759(12)	7646(9)	1980(5)	75(5)
C(3)	4731(19)	8322(14)	1169(7)	88(6)
C(2)	5768(17)	7500(15)	1026(7)	75(5)
N(2)	6806(13)	8064(12)	695(6)	91(5)
C(1)	5208(20)	6539(15)	689(9)	82(6)
O(1)	5587(21)	6411(18)	271(7)	157(8)
O(11)	4438(16)	6006(12)	935(7)	125(6)
C(12)	3822(24)	5130(17)	656(12)	148(11)
S(100)	−3164(5)	11106(5)	1307(2)	96(2)
O(110)	−1946(17)	11442(37)	1494(15)	143(22)
O(120)	−4178(24)	11120(33)	1683(11)	135(17)
O(130)	−3218(30)	10238(20)	944(10)	109(11)
O(111)	−2171(24)	11660(24)	1580(11)	78(9)
O(121)	−4264(23)	10744(32)	1582(14)	108(12)
O(131)	−2570(27)	10231(16)	1028(10)	89(9)
C(100)	−3721(19)	12139(13)	859(7)	266(30)
F(110)	−2640(31)	12384(39)	615(16)	188(21)
F(120)	−4160(35)	12917(25)	1165(12)	146(14)
F(130)	−4440(47)	11654(38)	512(16)	221(21)
F(111)	−3002(38)	12161(34)	442(12)	150(15)
F(121)	−3644(44)	13155(19)	1011(16)	179(17)
F(131)	−4943(22)	11964(32)	760(15)	154(13)
S(200)	528(6)	1249(7)	4597(2)	104(2)
O(210)	−817(9)	1400(14)	4668(5)	117(5)
O(220)	1324(17)	1374(21)	5041(5)	187(10)
O(230)	1048(13)	1784(15)	4157(5)	128(6)
C(200)	760(20)	−177(11)	4429(7)	248(26)
F(210)	1987(20)	−242(28)	4301(11)	136(11)
F(220)	−63(27)	−361(33)	4057(11)	156(13)
F(230)	529(35)	−680(32)	4873(10)	184(15)
F(211)	1886(30)	−574(56)	4546(22)	303(37)
F(221)	561(55)	−145(66)	3926(9)	343(43)
F(231)	−189(38)	−700(39)	4658(19)	240(22)
S(300)	2243(3)	2996(4)	2700(2)	81(1)
O(310)	1902(16)	3628(12)	3137(5)	136(6)
O(320)	3301(11)	2303(10)	2794(5)	96(4)
O(330)	1214(12)	2483(11)	2440(6)	111(5)
C(300)	2866(13)	3911(11)	2210(5)	133(10)
F(310)	3046(40)	3423(31)	1764(10)	149(16)
F(320)	2082(26)	4753(19)	2221(13)	125(10)
F(330)	3999(21)	4352(26)	2308(13)	116(11)
F(311)	3467(29)	3302(28)	1866(11)	148(16)
F(321)	1974(22)	4495(22)	1980(11)	129(11)
F(331)	3690(26)	4549(24)	2456(14)	150(17)
6				
Ru	8627(1)	10000	665(1)	33(1)
C(41)	8587(5)	11096(8)	1361(10)	35(5)
C(42)	8446(5)	11082(8)	−14(10)	35(5)
C(43)	8063(5)	10638(8)	−541(9)	42(6)
C(44)	7820(5)	10208(8)	306(14)	46(6)
C(45)	7961(5)	10222(7)	1681(13)	48(7)
C(46)	8344(5)	10666(8)	2208(8)	47(6)

Table 2 (continued)

Atom	x	y	z	U_{eq}
6				
C(411)	8996(8)	11587(11)	1986(23)	57(7)
C(412)	9350(11)	11896(20)	1022(31)	86(11)
C(413)	8760(16)	12233(16)	2589(37)	123(18)
C(441)	7376(8)	9755(13)	−235(30)	62(8)
C(31)	9181(5)	9335(7)	1854(10)	35(4)
C(32)	9441(5)	9803(8)	1120(13)	39(5)
C(33)	9333(6)	9840(8)	−265(13)	49(6)
C(34)	8966(6)	9408(9)	−916(10)	50(6)
C(35)	8706(5)	8940(8)	−182(14)	55(6)
C(36)	8813(5)	8903(7)	1203(14)	42(5)
C(3)	9277(8)	9340(10)	3388(18)	42(5)
C(2)	9572(6)	8679(9)	3962(16)	31(4)
N(2)	9523(6)	8647(9)	5411(14)	37(4)
C(1)	10109(7)	8701(10)	3609(18)	34(4)
O(1)	10176(6)	8741(9)	2423(14)	44(4)
Ru'	6383(1)	1085(1)	4480(1)	31(1)
C(51)	6423(5)	23(9)	3719(14)	56(7)
C(52)	6589(5)	9(9)	5080(13)	48(6)
C(53)	6989(5)	432(9)	5587(10)	52(6)
C(54)	7222(5)	869(8)	4732(14)	35(6)
C(55)	7056(5)	883(8)	3371(13)	48(7)
C(56)	6657(5)	460(9)	2864(10)	44(6)
C(511)	6034(8)	−490(11)	3081(23)	74(10)
C(512)	5647(13)	−709(21)	4038(32)	113(16)
C(513)	6291(14)	−1101(17)	2422(34)	91(12)
C(541)	7667(8)	1313(14)	5301(28)	57(7)
C(31')	5868(5)	1886(8)	3429(10)	28(4)
C(32')	6238(5)	2233(7)	4259(14)	52(6)
C(33')	6316(6)	2067(8)	5615(13)	52(6)
C(34')	6025(6)	1553(9)	6140(10)	62(8)
C(35')	5655(5)	1206(8)	5310(14)	46(6)
C(36')	5577(5)	1372(8)	3955(13)	47(6)
C(3')	5807(7)	2117(10)	1969(15)	34(4)
C(2')	5393(6)	1782(10)	1037(17)	34(4)
N(2')	5483(5)	2022(9)	318(14)	36(4)
C(1')	4869(7)	2013(10)	1367(18)	34(4)
O(1')	4810(6)	2151(8)	2506(13)	37(3)
S(100)	5791(3)	113(4)	8614(6)	54(2)
O(110)	5863(12)	280(13)	10025(11)	105(10)
O(120)	6228(5)	227(15)	7923(21)	98(10)
O(130)	5311(6)	343(12)	7983(24)	83(7)
C(100)	5771(9)	−836(7)	8555(22)	88(12)
F(110)	5644(13)	−1085(13)	7336(22)	150(12)
F(120)	5400(11)	−1055(15)	9225(34)	158(13)
F(130)	6169(10)	−1152(13)	9174(27)	128(10)
S(200)	9199(3)	10924(4)	−3562(6)	61(2)
O(210)	9073(9)	10774(13)	−4960(11)	83(7)
O(220)	8794(7)	10804(13)	−2754(19)	92(8)
O(230)	9681(6)	10682(16)	−2987(25)	101(9)
C(200)	9255(9)	11875(6)	−3533(20)	91(13)
F(210)	9337(11)	12099(14)	−2278(21)	130(10)
F(220)	9611(14)	12123(20)	−4224(36)	191(17)
F(230)	8811(9)	12140(12)	−3987(25)	119(9)
S(300)	7012(2)	1937(4)	9366(5)	45(2)
O(310)	7141(8)	1538(11)	8228(16)	70(6)
O(320)	6530(5)	2278(12)	9127(22)	71(6)
O(330)	7128(10)	1599(13)	10638(16)	88(8)
C(300)	7445(6)	2674(8)	9372(20)	85(12)
F(310)	7346(8)	3069(13)	8299(20)	100(8)
F(320)	7456(14)	3060(13)	10468(27)	150(13)
F(330)	7906(6)	2428(13)	9373(30)	126(10)
S(400)	7996(2)	9143(4)	−4306(7)	54(2)

Table 2 (continued)

Atom	x	y	z	U_{eq}
6				
O(410)	8467(6)	8777(12)	−4205(32)	110(10)
O(420)	7886(8)	9568(13)	−3184(18)	84(7)
O(430)	7835(10)	9579(14)	−5560(16)	87(7)
C(400)	7528(6)	8444(8)	−4333(22)	73(10)
F(410)	7063(7)	8653(14)	−4231(34)	161(14)
F(420)	7635(8)	8003(13)	−3329(27)	124(10)
F(430)	7586(13)	8029(13)	−5365(23)	128(10)

the suspension stirred for 24 h at reflux. The resulting precipitate was washed with CH_2Cl_2 and diethyl ether and dried in vacuum to deliver **6** (yield 73%). Light-brown crystals of **6** for X-ray analysis were obtained by recrystallisation from a CH_3OH/Et_2O solution followed by a CH_3NO_2/Et_2O solution. Anal. Found: C, 36.9; H, 3.5; N, 2.5; M = 1361.2. $C_{42}H_{46}N_2O_{14}F_6S_4Ru_2$ Calc.: C, 37.1; H, 3.4; N, 2.1%. FAB mass spectrum: m/z 1213 (8%) $[M - CF_3SO_3]^+$, 1063 (8%) $[M - 2CF_3SO_3]^+$, 912 (9%) $[M - 3CF_3SO_3]^+$, 780 (5%) $[M - 3CF_3SO_3 - \text{cymene}]^+$, 679 (7%) $[M - 3CF_3SO_3 - Ru(\text{cymene})]^+$, 529 (100%) $[M - 4CF_3SO_3 - Ru(\text{cymene})]^+$, 396 (58%) $[M - 4CF_3SO_3 - Ru(\text{cymene}) - \text{cymene}]^+$. ^1H NMR (CD_3NO_2): δ 1.49 (d, 12H, cymene), 2.70 (s, 6H, cymene), 3.20 (sp, 2H, cymene), 3.34 (dd, 2H, β-H), 3.47 (dd, 2H, β-H), 4.56 (dd, 2H, α-H), 7.11 (m, 14H, cymene + Ph), 7.20 (dd, 4H, Ph), 7.34 (s, NH). ^{13}C NMR (CD_3NO_2): δ 19.8, 22.9, 33.4 (cymene), 38.3 (β-*C*), 56.3 (α-*C*), 93.8, 95.0, 95.8, 96.2, 96.7, 97.5 (cymene + Ph), 113.3, 115.2 (cymene), 121.4 (q, *C*$F_3SO_3^-$), 124.4 (Ph), 187.9 (*C*ONH). IR: δ(NH) 3285m; ν(CO) 1674s; δ(NH) 1544w cm^{-1}.

2.2. X-ray structural analyses

Crystal and refinement data are summarised in Table 1. Unit-cell constants were determined for the crystals from least-squares fits to the settings of 25 reflections centred on a Siemens P4 diffractometer. Intensity data were collected on the diffractometer at varied scan rates in the ω mode (compounds **2** and **3**) or in the **θ–2θ** mode (compound **6**) for Mo Kα radiation. These were corrected for absorption on the basis of ψ scan information for selected reflections (compounds **2** and **3**) or empirically with DIFABS [14] after isotropic refinement of the non-hydrogen atoms (compound **6**). The structures were solved by use of direct methods and difference syntheses and refined against F^2 with hydrogen atoms at geometrically calculated positions. Rotational disorder was observed for one of the $CF_3SO_3^-$ anions of **2** [S(200)], two of the similar anions in **3** [S(200), S(300)] and the cymene carbon atoms C(412) and C(413) in **3**. Where required C, O and F atoms were assigned

site occupation factors of 0.5. Anisotropic temperature factors were introduced for those non-hydrogen atoms which were not disordered. The highest peaks (max. 2.41 e Å^{-3}) in the final difference synthesis for **6** all exhibit the same x and y coordinates as the ruthenium atoms Ru or Ru′ and are apparently artefacts caused by the pseudo-symmetrical relationship between these heavy atoms. They lie within 2.07 Å from atoms of non-disordered $CF_3SO_3^-$ anions and cannot therefore represent methanol solvent molecules. Weighting schemes were of the type $w = 1/[\sigma^2(F_o^2) + (aP)^2 + bP]$ with $P = [\max(F_o^2,0) + 2F_o^2]/3$. The following values of a and b were employed in the final refinement cycles: **2**, 0.065, 4.202; **3**, 0.115, 0.649; **6**, 0.010, 189.645. Structure solution and refinement were performed with the programs SHELXS [15] and SHELXL [16]. Fractional atomic coordinates and equivalent isotropic temperature factors are listed in Table 2. Additional crystallographic information is available from Fachinformationszentrum Karlsruhe, D-76344 Eggenstein-Leopoldshafen under the deposition numbers CSD-405455 **2**, 405457 **3**, 405456 **6**.

3. Discussion

Treatment of chloro-bridged ruthenium(II) dimers of the type $[\{RuCl(\eta^6\text{-arene})\}_2(\mu\text{-Cl})_2]$ with unprotected amino acids (HaaOH) in water or methanol at room temperature leads to facile formation of monomeric κ^2N,O chelated complexes $[RuCl(HaaO\text{-}\kappa^2N,O)(\eta^6\text{-arene})]$ [17–20]. κN coordinated compounds such as $[RuCl_2(\eta^6\text{-}C_6H_6)(HalaOMe\text{-}\kappa N)]$ (HalaOMe = L-alanine methyl ester) are obtained when the carboxylic acid function is protected as an alkyl ester [18]. In contrast to the tris(acetonitrile) complex $[RuCp^*(MeCN)_3]^+$, which delivers the entropically favoured sandwich complex as an insoluble product on treatment with free HpheOH in thf, the analogous reaction of the tris(solvent) starting material $[Ru(acetone)_3(\eta^6\text{-cymene})]^{2+}$ (**1**) leads to formation of a κ^2N,O coordinated compound in CH_2Cl_2. Under such conditions, bis(η-arene)Ru^{II} sandwich complexes can only be prepared for fully protected amino acids, as exemplified by $[Ru(\eta^6\text{-AcpheOMe})(\eta^6\text{-cymene})][CF_3SO_3]_2$ (**2**), the dication of which is depicted in Fig. 1. The dihedral angle defined by the planes of the coordinated arene ligands measures 1.6(4)° and the ruthenium atom is located nearly equidistantly from the ring centroids at distances of 1.717(4) (cymene) and 1.731(4) Å (AcpheOMe). The Ru–C distances fall in the narrow ranges 2.208–2.221 and 2.203–2.237 Å for the participating aromatic ring systems. As may be seen in Fig. 1, the η^6-coordinated amino acid derivative AcpheOMe is orientated in such a way that the C(31)–C(3) bond of its side chain is

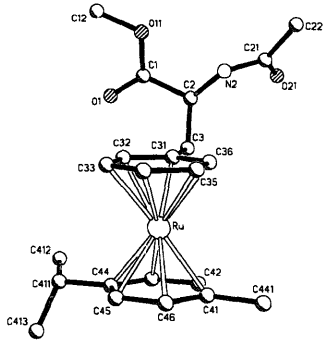


Fig. 1. Molecular structure of the cation $[Ru(\eta^6\text{-AcpheOMe})(\eta^6\text{-cymene})]^{2+}$ of **2**.

positioned effectively perpendicular to the C(44)–C(441) and C(41)–C(411) bonds of the cymene substituents, leading thereby to a minimum of steric interaction.

η^6-Coordination of half-protected or free amino acids can, however, be achieved for the $(\eta^6\text{-cymene})Ru^{II}$ fragment under strongly acid conditions. For instance, protonation of the amino nitrogen atom in $[H_2pheOMe]CF_3SO_3$ prevents the formation of a κN coordinated complex on treatment of this methyl ester with **1** in CH_2Cl_2. The off-white precipitate of $[Ru(\eta^6\text{-cymene})(\eta^6\text{-}H_2pheOMe)][CF_3SO_3]_3$ (**3**), obtained under these reaction conditions contains a trication, whose X-ray structure is displayed in Fig. 2. Structural details for this sandwich complex are very similar to those

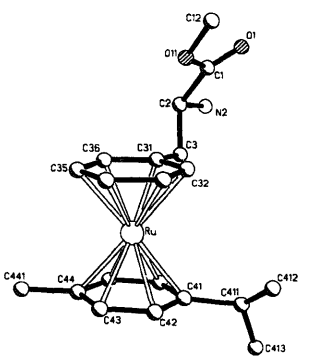


Fig. 2. Molecular structure of the cation $[Ru(\eta^6\text{-cymene})(\eta^6\text{-}H_2pheOMe)]^{3+}$ of **3**.

already discussed for **2**. For instance, the central metal atom is effectively equidistant [1.724(7) cymene ring, 1.720(7) Å phenyl ring] from the centroids of the η^6-coordinated aromatic ligands, whose planes are inclined at an angle of 2.0(6)° to one another. Once again, steric contacts between the aromatic substitutients are minimised by the adoption of a perpendicular siting for the cymene and phenyl ring systems. As demonstrated by their respective torsion angles C(2)–C(3)–C(31)–C(32) of 86.2(9) and −108.9(15)°, the C_α–C_β bonds of **2** and **3** corroborate this advantage by pointing away from the bis(arene)Ru^{II} sandwich. Participation of the protonated amino group in the H_2PheOMe complex in N–H···O hydrogen bonds to $CF_3SO_3^-$ leads to a dramatic change in the torsion angle C(31)–C(3)–C(2)–N(2) from 59(1) in **2** to 176(1)°. The IR spectrum of **3** contains two absorption bands at 1607 and 1536 cm^{-1}, values that are typical for a protonated amino group.

Satisfactory product yields of the η^6-coordinated complexes of AcpheOH and HpheOH, **4** and **5**, may be obtained by utilising trifluoroacetic acid as a solvent at higher temperature, a strategy originally proposed by Bennett and Matheson in the first published report of bis(arene)Ru^{II} complexes [10]. As observed for the H_2pheOMe complex **3**, protonation of the amino group in HpheOH under strongly acid conditions prevents its participation in the subsequent reaction with [Ru(acetone)$_3$(η^6-cymene)]$^{2+}$ (**1**), leading thereby to the preferred formation of the sandwich complex **5**. This compound may also be obtained by base-catalysed ester cleavage of **3** at a pH value of ca. 12. Somewhat surprisingly the product of this reaction exhibits a ^{1}H NMR spectrum identical to that of **5** as obtained by treatment of [Ru(acetone)$_3$(η^6-cymene)]$^{2+}$ with HpheOH in CF_3COOH. This finding and the observation of a pronounced ^{1}H NMR upfield shift (0.79 ppm) for the resonance of the amino protons of **5** in comparison to **3** suggests that the η^6-coordinated phenylalanine ligand is not protonated in the former complex. Further evidence for this conclusion is provided by the absence of typical δ(NH) IR bands for a protonated amino group in **5** in the range 1500–1610 cm^{-1} as found for **3** (1607, 1536 cm^{-1}). The required displacement of the weakly coordinating acetone ligands in **1** should also be favoured by their protonation in the trifluoroacetic acid reaction medium [10,11]. However, we found that employment of the non-coordinating solvent CH_2Cl_2 leads to better yields for the fully protected phenylalanine derivatives AcpheOMe and *cyclo*-(phephe) and avoids the problems associated with the coordination of CF_3COOH during the course of the reaction. The advantages of this solvent for the preparation of bis(arene)Ru^{II} complexes of polycyclic aromatic hydrocarbons have recently been discussed by Porter et al. [21].

The ^{1}H NMR resonances for the aromatic protons of the sandwich complexes **2**–**6** lie in the close ppm range 7.1–7.4. As reported for other bis(arene)Ru^{II} complexes containing the ligand, the cymene signals are shifted downfield (ca. 1.0 ppm) in comparison to the half-sandwich starting material **1** [12,21,22]. A slight upfield shift (ca. 0.2 ppm) is found for the aromatic resonances of the phenylalanine derivatives relative to those of the uncoordinated ligands. ^{13}C NMR data reveal a consistent pattern of upfield chemical shifts of ca. 20–30 ppm for the carbon atoms directly coordinated to the metal atom in comparison to those registered for the free aromatic systems. The resonances for the aromatic C atoms with alkyl substituents are registered between 111.1 and 115.7 ppm for the cymene ligands and 122.1 and 125.0 ppm for the phenylalanine derivatives. Whereas the remaining aromatic carbon atoms each give rise to a single resonance in **3** (nine signals), this is not the case for the other compounds which exhibit either six or seven resonances in the typical range (93.8–98.0 ppm). The methyl groups of the cymene isopropyl substituent in complexes **2**–**6** generate a ^{1}H NMR doublet, in accordance with unhindered rotation about the arene–carbon bond at room temperature. A broad resonance can be located in the range 7.20–7.34 for the amide proton in complexes **2**, **4** and **6** and the amino proton in **5**. This signal is shifted downfield to 8.04 ppm for the protonated amino group of the η^6-coordinated methyl ester [H_2pheOMe]$^+$ in **3**.

The feasibility of (η^6-cymene)Ru^{II} labelling of phenylalanine side chains peptides was tested by allowing *cyclo*-(phephe) to react with **1** under relatively mild conditions in the non-coordinating solvent CH_2Cl_2. Using a 1:2 molar ratio, two organometallic sandwich centres can be introduced into the resulting product [{Ru(η^6-cymene)}$_2${*cyclo*-(phephe)}][CF_3SO_3]$_4$ (**6**) in a satisfactory yield (56%). Interestingly, the asymmetric unit of the unit cell of **6** contains two independent tetracations, both of which (Figs. 3 and 4) exhibit

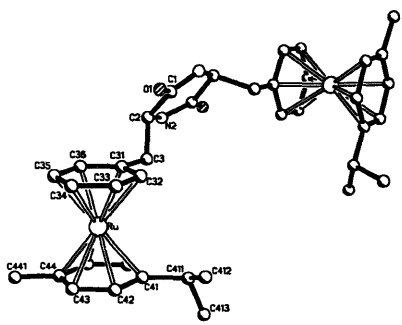


Fig. 3. Molecular structure of the first independent cation [{Ru(η^6-cymene)}$_2${*cyclo*-(phephe)}]$^{4+}$ of **6**.

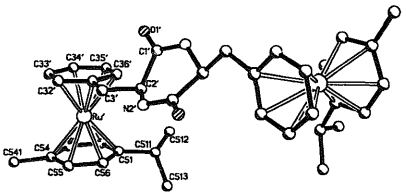


Fig. 4. Molecular structure of the second independent cation $[\{Ru(\eta^6\text{-cymene})\}_2\{cyclo\text{-(phephe)}\}]^{4+}$ of **6**.

crystallographic C_2 symmetry. The dimensions and relative ligand sitings of the bis(arene)Ru^{II} fragments are similar to those found in **2** and **3**. For instance, the distances of the Ru atoms from the ring centroids measure 1.702–1.730 Å and the C(31)–C(3) bonds of *cyclo*-(phephe) are positioned effectively perpendicular to the arene–carbon bonds of the cymene substituents. However, marked conformational differences are observed for the central six-membered rings of the dipeptides and the positions of their aromatic side chains. Whereas deviations from planarity for cation 1 (Fig. 3) are relatively limited (C1 0.05(2), C2 0.01(1), N2 −0.06(2) Å), a pronounced distortion towards a boat conformation (C1′ 0.14(2), C2′ −0.30(2), N2′ 0.16(2) Å) from the best least-squares plane is found for cation 2 (Fig. 4). Relevant torsion angles (with cation 2 in square brackets) are C1–C2–N2–C1a 7(2)° [−40(2)°], C2–N2–C1a–C2a −11(3)° [4(2)°], N2–C1a–C2a–N2a 4(2)° [34(2)°]. As demonstrated in Fig. 5, the bis(arene)Ru^{II} sandwich fragments of the independent cations are related to one another by a pseudo centre of symmetry in the crystal lattice, presumably in order to provide satisfactory packing. As the C2 atoms of the central dipeptide ring are chiral, this state of affairs can only be achieved by adoption of strikingly different torsion angles in the aromatic side chains (cation 2 in square brackets): N2–C2–C3–C31 −165(1)° [−171(1)°], C2–C3–C31–C36 75(2)° [2(2)°].

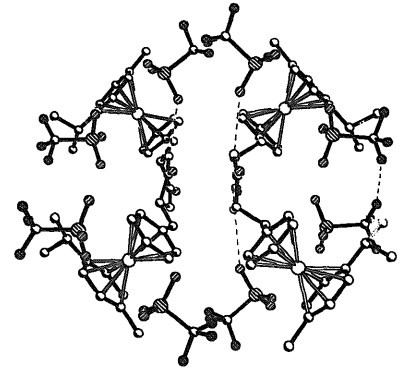


Fig. 5. Projection perpendicular to [001] of the packing of the independent cations of **6** as by a related pseudo centre of symmetry.

Preliminary investigations indicate that the (η^6-cymene)Ru^{II} fragment can influence the reactivity of both uncoordinated and η^6-coordinated phenylalanine derivatives. For instance, in an attempt to prepare a t-bocpheOH sandwich complex analogous to **4**, treatment of this N-protected phenylalanine derivative with **1** in CH_2Cl_2 was found to lead to cleavage of the t-boc group and precipitation of the free amino acid in quantitative yield. A remarkable, effectively quantitative spontaneous esterification of the free carboxylic acid function and formation of $[Ru(\eta^6\text{-AcpheOMe})(\eta^6\text{-cymene})][CF_3SO_3]_2$ (**2**) is observed when the η^6-AcpheOH complex **4** is dissolved in methanol and left to crystallise over a period of 1–2 days at room temperature. In contrast, no reaction occurs under similar conditions for the higher alcohols ethanol or isopropanol. Interestingly, esterification of the uncoordinated derivative Acphe can also be achieved, albeit at lower yield (20%), by treating this compound with $[Ru(\eta^6\text{-}C_6H_6)(\eta^6\text{-cymene})][CF_3SO_3]_2$ in methanol at room temperature for 7 days.

Our present results demonstrate that reaction of $[Ru(acetone)_3(\eta^6\text{-cymene})]^{2+}$ with HpheOH and its derivatives in CF_3COOH will deliver the entropically favoured bis(arene)Ru^{II} sandwich compounds rather than the alternative κN or $\kappa^2 N,O$ complexes. Preliminary findings confirm that an analogous organometallic labelling is also possible for the aromatic amino acids tyrosine and tryptophan [23].

References

[1] A. Vessières, M. Salmain, V. Philomin and G. Jaouen, *Immunoanal. Biol. Spec.*, *31* (1992) 9.
[2] M. Salmain, A. Vessières, P. Brossier, I.S. Butler and G. Jaouen, *J. Immunol. Methods*, *148* (1992) 65.
[3] G. Jaouen, A. Vessières and I.S. Butler, *Acc. Chem. Res.*, *26* (1993) 361.
[4] R.M. Moriarty, Y.-Y. Ku and U.S. Gill, *J. Chem. Soc., Chem. Commun.*, (1987) 1837.
[5] A.J. Pearson and K. Lee, *J. Org. Chem.*, *59* (1994) 2304.
[6] J.W. Janetka and D.H. Rich, *J. Am. Chem. Soc.*, *117* (1995) 10585.
[7] W.S. Sheldrick and A.J. Gleichmann, *J. Organomet. Chem.*, *470* (1994) 183.
[8] A.J. Gleichmann, J.M. Wolff and W.S. Sheldrick, *J. Chem. Soc., Dalton Trans.*, (1995) 1549.
[9] J.M. Wolff, A.J. Gleichmann, C. Schmidt and W.S. Sheldrick, *J. Inorg. Biochem.*, *59* (1995) 219.
[10] M.A. Bennett and T.W. Matheson, *J. Organomet. Chem.*, *175* (1979) 87.

[11] M.A. Bennett, T.W. Matheson, G.B. Robertson, W.L. Steffen and T.W. Turney, *J. Chem. Soc., Chem. Commun.*, (1979) 32.
[12] S. Suravajjala, J.R. Polam and L.C. Porter, *J. Organomet. Chem.*, *461* (1993) 201; *Organometallics*, *13* (1994) 37.
[13] M.A. Bennett and A.K. Smith, *J. Chem. Soc., Dalton Trans.*, (1974) 233; M.A. Bennett, T.N. Huang, T.W. Matheson and A.K. Smith, *Inorg. Synth.*, *21* (1982) 74.
[14] N. Walker and D. Stuart, *Acta Crystallogr.*, *A39* (1983) 158.
[15] G.M. Sheldrick, SHELXS 86, *A Program for Structure Determination*, Göttingen, 1986.
[16] G.M. Sheldrick, SHELXL 93, *A Program for Structure Refinement*, Göttingen, 1993.
[17] D.F. Dersnah and M.C. Baird, *J. Organomet. Chem.*, *127* (1977) C55.
[18] W.S. Sheldrick and S. Heeb, *Inorg. Chim. Acta*, *168* (1990) 93.
[19] D. Carmona, A. Mendoza, F.J. Lahoz, L.A. Oro, M.P. Lamata and E. San Jose, *J. Organomet. Chem.*, *396* (1990) C17.
[20] R. Krämer, K. Polborn, H. Wanjek, I. Zahn and W. Beck, *Chem. Ber.*, *123* (1990) 767.
[21] L.C. Porter, J.R. Polam and S. Bodige, *Inorg. Chem.*, *14* (1995) 998.
[22] S. Chem, V. Carperos, B. Noll, R.J. Swope and M. Rakowski DuBois, *Organometallics*, *14* (1995) 1221.
[23] J.M. Wolff and W.S. Sheldrick, unpublished results.