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Preparation and characterization of d^6 tungsten compounds with amino acid derivatized diimine ligands and preparation of dipeptide derivatives using peptide coupling agents

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Abstract

Attempts to prepare dipeptide compounds from organometallic N-substituted amino acids are reported. Condensation of pyridine-2-carboxaldehyde, α-amino acids (H-L-Ala-OH or H-L-Asp-OH) and $W(CO)_4(pip)_2$ leads to formation of $W(CO)_4$(pyca-Et) (**1**) (pyca refers to the α-diimine fragment, $C_5H_4NCH{=}N$) following decarboxylation of one or two equivalents of CO_2. This decarboxylation does not occur for β-alanine or GABA (γ-aminobutyric acid). Coupling of [Hpip][$W(CO)_4$(pyca-β-Ala-O)] (**2**) or [Hpip][$W(CO)_4$(pyca-GABA-O)] (**3**) to amino acid esters, H-L-Ala-OEt, or H-L-Val-OMe, using the standard 1,3-dicyclohexylcarbodiimide (DCC), 1-hydroxybenzotriazole (HOBt) procedure produced four new dipeptide compounds, **4**–**7**. The reactions proceed in good yield and compounds were characterized spectroscopically. The dipeptide complex, $W(CO)_4$(pyca-Ala-Ala-OMe) (**8**), was prepared by reaction of $W(CO)_4(pip)_2$ with H-L-Ala-L-Ala-OMe and pyridine-2-carboxaldehyde. In addition the molecular structure of $W(CO)_4$(pyca-β-Ala-Val-OMe) (**5**) is reported.

Keywords: Amino acid; Crystal structure; Diimine; Tungsten

1. Introduction

Incorporation of biological ligands [1–3], especially amino acids or peptides [4,5], into organometallic systems has become a focus of chemists in recent years. The motivations for this focus range from the excitement of creating organometallic compounds with unusual ligands containing multiple and diverse functional groups, to the search for biological and medical applications [6,7].

Our group has concentrated on incorporating amino acid esters in diimine ligands as a way to create tightly binding ligands for organometallic centers. The first report of this chemistry focused on $M(CO)_4$(pyca-R) compounds (M = Cr, Mo, W; pyca refers to the pyridine-2-carbaldehyde imine fragment, $C_5H_4NCH{=}N$; R refers to the amino acid ester) such as $Mo(CO)_4$(pyca-Val-OMe) [8]. This work demonstrated that the α-diimine ligand, with the nitrogen of the amino acid ester contributing to the formation of the exocyclic imine, produces stable group 6 d^6 compounds. The pyca-R amino acid ester ligand set was also successfully utilized to make $Re(CO)_3Cl$(pyca-R) compounds. When chiral amino acid esters were employed, diastereomers in unequal populations were produced because of the presence of a stereogenic metal center [9]. We recently extended this work to molybdenum and tungsten compounds with corresponding diazabutadiene ligands created from the condensation of glyoxal and an amino acid ester [10]. It was observed that employing NEt_3 to remove HCl from the amino acid ester during the synthesis

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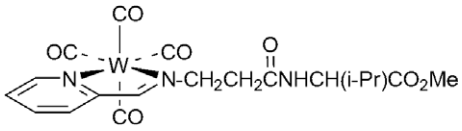
led to racemization of the α-carbon. Crystal structures of two diastereomers of $Mo(CO)_4$(dab-Asp(OMe)-OMe) supported this observation. Other researchers have examined organometallic compounds with pyridine-based diimine ligands for the possible development of metal-based pharmaceuticals. In particular thiosemicarbazones derived from 2- or 4-acetylpyridine, 2-pyridineformamide and 2,2′-dipyridyl ketone have been used in the creation of a variety of monomeric and dimeric compounds utilizing the $M(CO)_3^+$ (M = Tc, Re) fragment [11–14].

We were interested in extending these studies to examine whether group 6 compounds using the pyridine-2-carbaldehyde imine ligand with amino acids instead of amino acid esters could be created. The ultimate goal was to determine if dipeptide compounds could be prepared via standard peptide coupling methods with the $W(CO)_4$(pyca) moiety as an organometallic N-protecting group. Organometallic N-protecting groups have been the subject of previous studies because of the possible advantages they can offer including the color or lipophilic character of the protecting group. The ferrocenyl methyl (Fem) residue has been the most extensively studied [15,16]. It can be introduced without racemization of the amino acid, it survives peptide coupling reactions, and the yellow color of the protecting group is an aid to chromatographic separation. Some group 6 d^6 compounds have been examined as protecting groups as well. Aminocarbene compounds are formed by aminolysis of $[(CO)_5M{=}CR(COCH_3)]$ (M = Cr, W) with amino acid esters [17] and *cis*-$(OC)_4Re(CH_3CO)_2H$ condenses with amino acid esters to create the corresponding β-ketoimine derivatives [18,19].

Herein we report that the initial attempt to prepare diimine ligands based on α-amino acids led to decarboxylation. Reactions of mixtures of $W(CO)_4(pip)_2$ (pip = piperidine) and pyridine-2-carboxaldehyde with alanine or aspartic acid each gave $W(CO)_4$(pyca-Et) (**1**) due to loss of one or two molecules of CO_2, respectively. This was confirmed independently by creation of **1** using H_2NEt. A recent report of similar decarboxylation reactions has been published for the corresponding molybdenum compounds [20]. The reactions using the β- and γ-amino acids, β-alanine and GABA (γ-aminobutyric acid), showed that piperidinium salts with a pendant carboxylic acid, [Hpip][$W(CO)_4$-(pyca-$(CH_2)_n$-CO_2)] ($n = 2$ or 3, compounds **2** and **3**, respectively), could be obtained under the same conditions in good yield without loss of CO_2.



5 = $W(CO)_4$(pyca-β-Ala-Val-OMe)

Fig. 1. Representative structure of **5**.

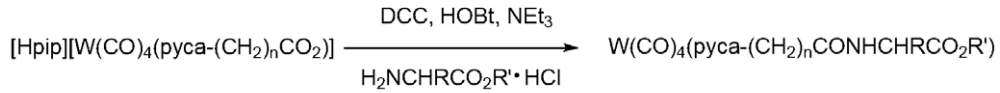
The N-protected amino acid piperidinium salts, **2** and **3**, were successfully coupled with L-alanine ethyl ester or L-valine methyl ester to create four new single enantiomer organometallic dipeptide compounds, **4**–**7** (see Fig. 1 and Scheme 1). In addition $W(CO)_4$(pyca-Ala-Ala-OMe) (**8**) was prepared as a single enantiomer by direct reaction of the dipeptide, H-L-Ala-L-Ala-OMe, with $W(CO)_4(pip)_2$ and pyridine-2-carboxaldehyde. Finally we report the structural characterization of **5**. Preliminary accounts of the decarboxylation [21] and peptide coupling [22] processes were presented previously.

2. Results and discussion

2.1. Attempted syntheses of W(CO)4(pyca-Ala-OH) and W(CO)4(pyca-Asp-OH): preparation of W(CO)4(pyca-Et) (1)

Reflux of one equivalent each of $W(CO)_4(pip)_2$, pyridine-2-carboxaldehyde and alanine in methanol led to the rapid change in solution color from light-yellow to a deep, red color. Column chromatography followed by removal of the solvent led to a reddish-brown solid. Elemental analysis and spectroscopic characterization were consistent with formulation of this compound as **1**. The reaction using aspartic acid as the amino acid was also attempted. Isolation and purification again resulted in a compound with spectroscopic properties consistent with those expected for **1**.

To verify that these compounds were indeed **1**, this compound was prepared using H_2NEt as the added amine. The



No.	n =	Comp.
2	2	[Hpip][$W(CO)_4$(pyca-β-Ala-O]
3	2	[Hpip][$W(CO)_4$(pyca-GABA-O]

No.	n =	R =	R' =	Comp.
4	2	Me	Et	$W(CO)_4$(pyca-β-Ala-Ala-OEt)
5	2	i-Pr	Me	$W(CO)_4$(pyca-β-Ala-Val-OMe)
6	3	Me	Et	$W(CO)_4$(pyca-GABA-Ala-OEt)
7	3	i-Pr	Me	$W(CO)_4$(pyca-GABA-Val-OMe)

Scheme 1. General reaction scheme and numbering system for compounds **2**–**7**.

spectroscopic properties (^{1}H NMR, ^{13}C NMR, IR) of the compounds prepared with H_2NEt were identical with those of the compounds isolated from the reactions using alanine and aspartic acid proving that this was the product of each reaction. The common product shared for reactions of these three amines is shown in Scheme 2.

The reactions with alanine and aspartic acid can be characterized as decarboxylations with the loss of one and two equivalents of CO_2, respectively. This was previously observed in a recent article for related molybdenum compounds [20] where it was compared to the amino acid decarboxylations catalyzed by the vitamin B_6 coenzyme, pyridoxal phosphate [23–26]. The coenzyme is also a pyridine aldehyde that undergoes condensation reactions with amino acids prior to decarboxylation. The common features are that the coenzyme is protonated at the pyridine nitrogen while the metal complexes have the diimine bound to the metal through a dative bond. Each structure generates an electron rearrangement promoted by π-electron delocalization initiated by protonation or dative bonding to a $W(CO)_4$ fragment. For the appropriate electron flow leading to CO_2 loss the imine nitrogen and the CO_2 are separated by one alkyl carbon [20].

2.2. Synthesis of [Hpip][W(CO)$_4$(pyca-β-Ala-O)] (2) and [Hpip][W(CO)$_4$(pyca-GABA-O)] (3)

The attempt to create organometallic amino acid conjugates succeeded when β-alanine or GABA was used as the amino acid. Deep red-purple colored solutions were produced during the reaction. They can be isolated at this point as the spectroscopically identified carboxylic acids, however elemental analysis gave poor results. The procedure was modified so that a few drops of piperidine were added to the eluate to convert the carboxylic acid to the piperidinium salt. The compounds are significantly less soluble in non-polar solvents and chromatography requires some methanol to elute the compounds. Removal of the solvent produced analytically pure piperidinium carboxylate compounds **2** and **3** as black powders. These amino acid derivatives do not undergo decarboxylation because the extra methylene group or groups apparently prevents the structural arrangement required to induce decarboxylation. The related β-alanine and 4-aminobenzoic acid derivatives of $Mo(CO)_4$(pyca-R) are also reported to be stable toward decarboxylation [20].

2.3. Synthesis of 4–7

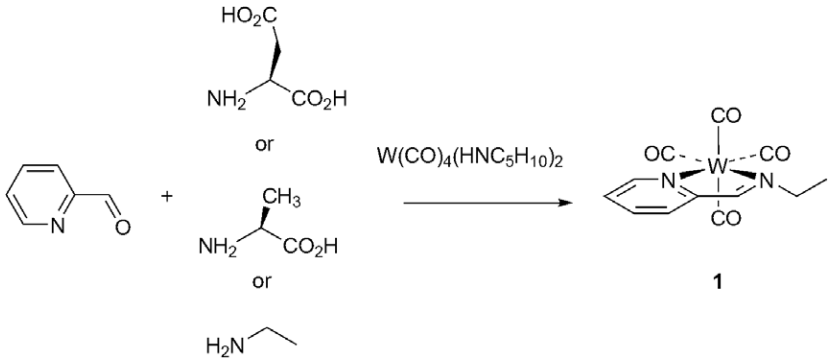
Compounds **2** and **3** were used in the preparation of N-derivatized organometallic dipeptides **4**–**7**. The reactions proceed in moderate yield in CH_2Cl_2 overnight in the presence of DCC (1,3-dicyclohexylcarbodiimide) and HOBt (1-hydroxybenzotriazole) (Scheme 1) [27,28]. The success of this reaction and the ease of workup indicates that this organometallic system can be used as a protecting group during peptide coupling, but only if the N-protected amino acid can be prepared. Although dipeptide compounds with α-amino acids as the proximal amino acid could not be prepared using peptide coupling, they can be readily prepared by refluxing a dipeptide ester, pyridine-2-carboxaldehyde and $W(CO)_4(pip)_2$. This was demonstrated by the synthesis of **8** using H-Ala-Ala-OMe · HCl.

2.4. Spectroscopic characterization

Infrared spectra of all derivatives show four metal carbonyl bands with the pattern and energies expected for a *cis*-substituted tetracarbonyl complex [29]. Compounds **4**–**8** also show two weaker bands for the ester and the amide carbonyls at around 1735 and 1670 cm^{-1}, respectively.

The ^{1}H and ^{13}C NMR spectra reported are consistent with the proposed formulas and the expected stereochemistry. The metal carbonyl peaks in the ^{13}C NMR are diagnostic for the stereochemistry of these compounds. Compounds **1**–**3** show one upfield resonance assigned to the two mutually *trans* carbonyls (CO_{trans}) which are equivalent due to a plane of symmetry. The other two peaks are assigned to the two *cis* carbonyls (CO_{cis}). Each is *trans* to a chemically unique imine nitrogen. The ^{1}H and ^{13}C NMR resonances for the imine portion of the molecule show resonances expected for single isomer compounds and occur in the expected portion of the spectra.

In contrast four of the five dipeptides reported display two ^{13}C signals for the *trans* metal carbonyl despite the relative separation of the chiral center from the metal center



Scheme 2. Preparation of **1** via three different amines.

(**4** shows only one signal for the two *trans* carbonyls). This is ascribed to the effect of the chiral amino acid(s) in each compound and the associated loss of planar symmetry and has been observed previously for related group 6 compounds [8]. The remaining resonances occur in the expected regions. It is especially important to note that only one resonance is observed in the ^{1}H and ^{13}C spectra for the α′-CH group (α′ refers to the distal amino acid ester). This was previously shown to be a sensitive measure of the presence of diastereomers potentially formed by racemization [9]. The observation of unique resonances proves that a single diastereomer is isolated in each synthesis supporting the idea that racemization is not occurring.

2.5. Molecular structure of $W(CO)_4$(pyca-β-Ala-Val-OMe) (**5**)

Crystals of **5** were grown by layering hexanes over a solution of CH_2Cl_2 containing the compound and allowing the layers to slowly mix. The compound crystallized in the space group $P2_12_12_1$ with two molecules in the asymmetric unit. The metrical data are similar for each structure. Data are presented for only one of the molecules in the asymmetric unit since the two molecules are identical with the exception of the conformation of the peptide chain. The molecular structure is illustrated in Fig. 2. Crystal data are given in Table 1 and relevant bond lengths and angles are found in Table 2.

The compound displays a slightly distorted octahedral geometry around the tungsten largely due to the 72.3(3)° bite angle measured for the diimine ligand. This value is within a degree of the bite angles observed for the three related $Mo(CO)_4$(diimine) compounds with amino acid esters we have previously characterized by crystallography [8,10]. The two mutually *trans* COs bend away from the diimine ligand at an angle of 171.0(5)°. The pyridine and imine portions of the diimine ligand are co-planar as required by the demands of ligand π conjugation and metal–ligand backbonding. The 1.42(2) and 1.34(1) Å distances measured for C(13)–C(14) and C(14)–N(2), respectively, verify the conjugation of the ligand. The dipeptide chain is aligned along the axis of the *trans* COs, a tendency observed previously for other structurally characterized group 6 and 7 diimine compounds created from amino acid ester condensation [8–10]. The valine amino acid maintains its expected L-conformation in the complex showing that the stereochemistry has been retained during the synthesis of this compound. The value of the absolute structure factor confirms that this is the only diastereomer present.

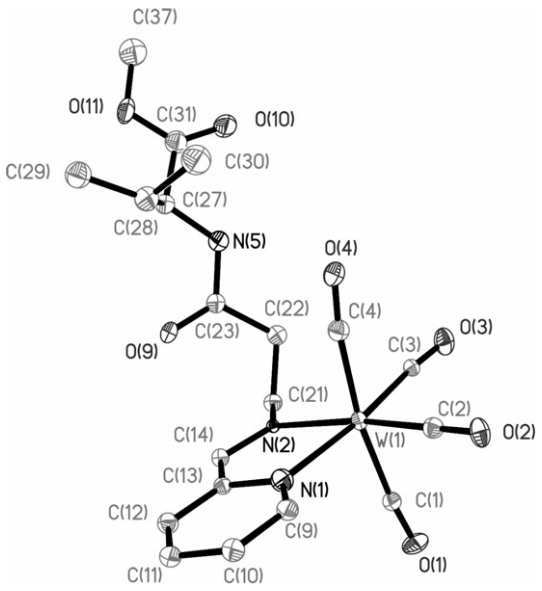


Fig. 2. Molecular structure of **5** with 30% ellipsoids.

Table 1
Crystal data and structure refinement for **5**

Empirical formula	$C_{19}H_{21}N_3O_7W$
Formula weight	587.24
Temperature (K)	100(2)
Wavelength (Å)	0.71073
Crystal system	Orthorhombic
Space group	*P*2(1)2(1)2(1)
Unit cell dimensions	
a (Å)	8.742(3)
b (Å)	9.491(3)
c (Å)	51.289(17)
Volume (Å^3)	4255(3)
Z	8
Density (calculated) (Mg/m^3)	1.833
Absorption coefficient (mm^{-1})	5.474
F(000)	2288
Crystal size (mm^3)	0.20 × 0.10 × 0.03
θ Range for data collection (°)	1.59–28.32
Index ranges	$-11 \leqslant h \leqslant 11$, $-12 \leqslant k \leqslant 12$, $-68 \leqslant l \leqslant 68$
Reflections collected	37,773
Independent reflections [R_{int}]	10,160 [0.0753]
Completeness to $\theta = 28.32°$	97.9%
Absorption correction	SADABS
Maximum and minimum transmission	0.8530 and 0.4073
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	10,160/264/547
Goodness-of-fit on F^2	1.191
Final *R* indices [$I > 2\sigma(I)$]	$R_1 = 0.0660$, $wR_2 = 0.1165$
R indices (all data)	$R_1 = 0.0772$, $wR_2 = 0.1198$
Absolute structure parameter	0.04(2)
Largest difference in peak and hole (e Å^{-3})	2.214 and −4.711

2.6. Summary

Treatment of $W(CO)_4(pip)_2$ with pyridine-2-carboxaldehyde and the α-amino acids, H-L-Ala-OH or H-L-Asp-OH, leads to decarboxylation of the amino acid and formation of **1**. The identity of this compound was confirmed by preparing **1** using H_2NEt as the amine. Use of a β- or γ-amino acid led to the undecarboxylated products **2** and **3**. These organometallic N-derivatized amino acids were coupled to amino acid esters using DCC/HOBt to assist the coupling.

Table 2
Bond lengths (Å) and angles (°) for **5**

Bond lengths	
C(1)–W(1)	2.019(11)
C(2)–W(1)	1.964(11)
C(3)–W(1)	1.989(11)
C(4)–W(1)	2.013(12)
C(13)–N(1)	1.388(14)
C(13)–C(14)	1.416(15)
C(14)–N(2)	1.340(13)
C(15)–N(3)	1.348(14)
C(23)–O(9)	1.221(13)
C(23)–N(5)	1.359(14)
C(27)–N(5)	1.442(14)
C(27)–C(28)	1.500(16)
C(31)–O(10)	1.194(14)
C(31)–O(11)	1.302(14)
N(1)–W(1)	2.249(10)
N(2)–W(1)	2.195(8)
Bond angles	
C(2)–W(1)–C(3)	92.2(4)
C(2)–W(1)–C(4)	87.0(5)
C(3)–W(1)–C(4)	81.3(4)
C(2)–W(1)–C(1)	89.6(5)
C(3)–W(1)–C(1)	90.5(4)
C(4)–W(1)–C(1)	171.0(5)
C(2)–W(1)–N(2)	168.8(4)
C(3)–W(1)–N(2)	98.9(4)
C(4)–W(1)–N(2)	95.6(4)
C(1)–W(1)–N(2)	89.3(4)
C(2)–W(1)–N(1)	96.6(4)
C(3)–W(1)–N(1)	171.0(4)
C(4)–W(1)–N(1)	97.4(4)
C(1)–W(1)–N(1)	91.3(4)
N(2)–W(1)–N(1)	72.3(3)

The corresponding dipeptides **4**–**7** were isolated in modest yield demonstrating that organometallic compounds can withstand these coupling conditions. Spectroscopic data and the crystal structure of **5** confirmed the structures of these compounds and confirmed that only one enantiomer is obtained. While these highly colored compounds with an N-protecting group are intriguing, the inability to prepare α-amino acid derivatized compounds such as $W(CO)_4$(pyca-Ala-OH) will likely limit the use of the $W(CO)_4$(pyca) moiety as a protecting group.

3. Experimental

3.1. Spectroscopic measurements

NMR spectra were recorded on a Varian 400 MHz spectrometer. IR spectra were recorded on a Nicolet Series II Magna-IR 750 spectrometer. Elemental Analysis were performed by Atlantic Microlab of Norcross, GA 30091.

3.2. Materials

Starting materials were obtained from commercial sources and were used without further purification. Chiral amino acids, amino acid esters and the dipeptide utilized were all single enantiomer compounds. All solvents were degassed prior to use and a nitrogen atmosphere was used for all syntheses. $W(CO)_4(pip)_2$ was prepared by the literature procedure [29].

3.3. Synthesis of $W(CO)_4$(pyca-Et) (**1**)

Method 1: $W(CO)_4(pip)_2$ (0.500 g, 1.07 mmol), pyridine-2-carboxaldehyde (0.115 g , 1.07 mmol) and H-L-Ala-OH (0.0952 g, 1.07 mmol) were added to 20 mL of degassed methanol in a Schlenk flask. The solution was brought to reflux producing a deep red color. After 1 h, the solvent was removed. Flash chromatography using 1:1 ethyl acetate:hexanes eluted several minor colored impurity bands followed by a deep red band that was collected. The solvent was removed. The resulting solid was collected in 38% yield.

Method 2: $W(CO)_4(pip)_2$ (0.500 g, 1.07 mmol), pyridine-2-carboxaldehyde (0.115 g, 1.07 mmol) and H-L-Asp-OH (0.143 g, 1.07 mmol) were added to 20 mL of degassed methanol in a Schlenk flask. The solution was brought to reflux producing a deep red color. After 1 h, the solvent was removed. Flash chromatography using 1:1 ethyl acetate:hexanes eluted several minor colored impurity bands followed by a deep red band that was collected. The solvent was removed. The resulting solid was collected in 30% yield.

Method 3: Pyridine-2-carboxaldehyde (0.115 g, 1.07 mmol) was added to 20 mL of degassed methanol in a Schlenk flask. H_2NEt was bubbled into the solution for 5 min and the solution was warmed for 10 min. $W(CO)_4(pip)_2$ (0.500 g, 1.07 mmol) was added causing the solution to darken. The solution was brought to reflux for 1 h. The solvent was removed and the residue was dissolved in CH_2Cl_2. The solution was washed three times each with 1 M HCl, saturated $NaHCO_3$, then water. The organic layer was dried with magnesium sulfate, filtered and reduced in volume. Hexane was layered over the surface and the flask was placed in the refrigerator overnight. Filtration left a dark red-orange solid which was isolated in 26% yield.

3.3.1. $W(CO)_4$(pyca-Et) (**1**)

IR (CH_2Cl_2): 2015 (s), 1908 (vs), 1885 (sh), 1838 (s) cm^{-1}. Anal. Calc. for $C_{12}H_{10}N_2O_4W$; C, 33.51; H 2.34; N 6.51. Found: C, 33.67; H, 2.43; N, 6.56%. ^1H NMR ($CDCl_3$): δ 9.25 (d, $^3J = 5.5$ Hz, 1H, *H* on py), 8.77 (s, 1H, N=C*H*), 7.91 (m, 1H, *H* on py), 7.79 (d, $^3J = 7.8$ Hz, 1H, *H* on py), 7.35 (m, 1H, *H* on py), 4.25 (q, $^3J = 7.3$ Hz, 2H, CH_2), 1.64 (t, $^3J = 7.3$ Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$): δ 217.3 (CO_{cis}), 215.3 (CO_{cis}), 198.6 (CO_{trans}), 162.5 (C=N), 155.7 (C on py), 153.0 (C on py), 136.8 (C on py), 127.4 (C on py), 126.7 (C on py), 61.6 (CH_2), 18.2 (CH_3).

3.4. Synthesis of [Hpip][$W(CO)_4$(pyca-β-Ala-O)] (**2**) and [Hpip][$W(CO)_4$(pyca-GABA-O)] (**3**)

In a representative reaction $W(CO)_4(pip)_2$, (0.495 g, 1.06 mmol), γ-aminobutyric acid (0.109 g, 1.06 mmol) and

pyridine-2-carboxaldehyde (0.119 g 1.07 mmol) were added to 25 mL of degassed methanol. The solution was brought to reflux for 45 min. During this time the color changed from yellow to deep red. The compound was purified via flash chromatography on silica gel. Removal of several by-products was achieved with ethyl acetate. The product band was eluted using 1:1 ethyl acetate:methanol. Solvent was removed by rotary evaporator producing a dark solid. The solid was dissolved in CH_2Cl_2. Five drops of piperidine were added and several mL of hexane were added, but not enough to cause precipitation. A stream of N_2 over the top of the solution led to precipitation of the product after several hours. The product was filtered and dried overnight under vacuum resulting in **3** as a black powder.

3.4.1. [Hpip][W(CO)$_4$(pyca-β-Ala-O)] (**2**)

Yield: 65%. IR (nujol mull) 2003 (s), 1887 (s), 1851 (s), 1813 (s) cm^{-1}. Anal. Calc. for $C_{18}H_{21}N_3O_6W$: C, 38.66; H, 3.79; N, 7.51. Found: C, 38.06; H, 4.07; N, 7.60%. ^{1}H NMR ($CDCl_3$): δ 9.24 (d, $^3J = 5.2$ Hz, 1H, *H* on py), 8.92 (s, 1H, N=C*H*), 7.92 (m, 1H, *H* on py), 7.90 (d, $^3J = 8.1$ Hz, 1H, *H* on py), 7.34 (m, 1H, *H* on py), 4.60 (v br, 2H, NH_2 on Hpip$^+$), 4.40 (t, $^3J = 6.4$ Hz, 2H, α-CH_2), 3.08 (m, 4H, CH_2 on Hpip$^+$), 2.95 (t, $^3J = 7.2$ Hz, 2H, β-CH_2), 1.76 (m, 4H, CH_2 on Hpip$^+$), 1.68 (m, 2H, CH_2 on Hpip$^+$). ^{13}C NMR ($CDCl_3$): δ 217.4 (CO_{cis}), 215.6 (CO_{cis}), 207.4 (CO_{trans}), 179.2 (COO), 163.5 (C=N), 155.3 (C on py), 152.7 (C on py), 136.5 (C on py), 127.4 (C on py), 126.1 (C on py), 64.3 (α-*C*H_2), 44.5 (C on Hpip$^+$), 28.4 (β-*C*H_2), 23.2 (C on Hpip$^+$), 22.6 (C on Hpip$^+$).

3.4.2. [Hpip][W(CO)$_4$(pyca-GABA-O)] (**3**)

Yield: 71%. IR (nujol mull) 2001 (s), 1853 (s), 1803 (s) cm^{-1}. Anal. Calc. for $C_{19}H_{23}N_3O_6W$: C, 39.81; H, 4.04; N, 7.33. Found: C, 39.39; H, 4.34; N, 7.33%. ^{1}H NMR ($CDCl_3$): δ 9.22 (d, $^3J = 5.1$ Hz, 1H, *H* on py), 8.80 (s, 1H, N=C*H*), 7.93 (m, 1H, *H* on py), 7.85 (d, $^3J = 8.2$ Hz, 1H, *H* on py), 7.38 (m, 1H, *H* on py), 4.50 (v br, 2H, NH_2 on Hpip$^+$), 4.24 (t, $^3J = 6.6$ Hz, 2H, α-CH_2), 3.06 (m, 4H, CH_2 on Hpip$^+$), 2.35 (t, $^3J = 7.0$ Hz, 2H, γ-CH_2), 2.27 (m, 2H, β-CH_2), 1.79 (m, 4H, CH_2 on Hpip$^+$), 1.63 (m, 2H, CH_2 on Hpip$^+$). ^{13}C NMR ($CDCl_3$): δ 217.2 (CO_{cis}), 215.2 (CO_{cis}), 207.2 (CO_{trans}), 179.0 (COO), 163.9 (C=N), 155.6 (C on py), 152.9 (C on py), 136.7 (C on py), 127.7 (C on py), 126.7 (C on py), 66.3 (α-*C*H_2), 44.5 (C on Hpip$^+$), 33.9 (CH_2), 28.6 (CH_2), 23.0 (C on Hpip$^+$), 22.8 (C on Hpip$^+$).

3.5. Synthesis of **4**–**7**

In a reaction that demonstrates this procedure, [Hpip]-[W(CO)$_4$(pyca-β-Ala-O)] (**2**) (0.200 g, 0.424 mmol), H-Val-OMe · HCl (0.166 g, 1.27 mmol) and NEt_3 (0.256 g, 2.54 mmol) were added to 10 mL of degassed CH_2Cl_2 in a Schlenk flask. DCC (0.338 g, 1.27 mmol) and HOBt (0.171 g, 1.27 mmol) were added. The mixture was stirred overnight. Solvent was removed. Flash chromatography of the residue on silica gel produced a dark red-purple band that eluted with 1:2 ethyl acetate:hexane. Compound **5** was recrystallized from methylene chloride/hexane yielding a dark solid. Preparation of the other derivatives occurred in a similar fashion.

3.5.1. W(CO)$_4$(pyca-β-Ala-Ala-OEt) (**4**)

Yield: 60%. IR (CH_2Cl_2): 2008 (s), 1898 (vs), 1881 (sh), 1834 (s), 1734 (m), 1675 (m) cm^{-1}. Anal. Calc. for $C_{18}H_{19}N_3O_7W$: C, 37.72; H, 3.34; N, 7.33. Found: C, 37.84; H, 3.41; N, 7.35%. ^{1}H NMR ($CDCl_3$): δ 9.21 (d, $^3J = 5.5$ Hz, 1H, *H* on py), 8.87 (s, 1H, N=C*H*), 7.92 (m, 1H, *H* on py), 7.81 (d, $^3J = 7.8$ Hz, 1H, *H* on py), 7.39 (m, 1H, *H* on py), 6.15 (d, $^3J = 7.4$ Hz, 1H, O=C–N–*H*), 4.45 (m, 2H, α-CH_2), 4.42 (m, 1H, α′-C*H*), 4.09 (q, $^3J = 7.1$ Hz, 2H, CH_2CH$_3$), 3.08 (m, 2H, β-CH_2), 1.28 (d, $^3J = 7.4$ Hz, 3H, CHCH_3), 1.22 (t, $^3J = 7.1$ Hz, 3H, CH$_2$CH_3). ^{13}C NMR ($CDCl_3$): δ 216.4 (CO_{cis}), 215.3 (CO_{cis}), 198.5 (CO_{trans}), 172.4 (COO), 169.5 (O=C–N), 166.0 (C=N), 153.0 (C on py), 136.9 (C on py), 136.8 (C on py), 127.9 (C on py), 126.8 (C on py), 62.1 (CH_2), 62.0 (CH_2), 48.5 (α′-CH), 34.1 (CH_2), 18.2 (CHCH$_3$), 14.2 (CH$_2$*C*H$_3$).

3.5.2. W(CO)$_4$(pyca-β-Ala-Val-OMe) (**5**)

Yield: 51%. IR (CH_2Cl_2): 2008 (s), 1898 (vs), 1880 (sh), 1836 (s) 1740 (m), 1684 (m) cm^{-1}. Anal. Calc. for $C_{19}H_{21}N_3O_7W$: C, 38.86; H, 3.60; N, 7.16. Found: C, 38.86; H, 3.75; N, 7.29%. ^{1}H NMR ($CDCl_3$): δ 9.22 (d, $^3J = 5.5$ Hz, 1H, *H* on py), 8.86 (s, 1H, N=C*H*), 7.91 (m, 1H, *H* on py), 7.80 (d, $^3J = 7.8$ Hz, 1H, *H* on py), 7.39 (m, 1H, *H* on py), 6.07 (d, $^3J = 8.6$ Hz, 1H, O=C–N–*H*), 4.47 (m, 2H, α-CH_2), 4.41 (dd, $^3J = 8.6$ Hz, $^3J = 5.5$ Hz, 1H, α′-C*H*), 3.62 (s, 3H, OCH_3), 3.09 (m, 2H, β-CH_2), 2.04 (m, 1H, C*H*(CH$_3$)$_2$), 0.77 (d, $^3J = 7.0$ Hz, 3H CH(CH_3)$_2$), 0.75 (d, $^3J = 7.0$ Hz, 3H, CH(CH_3)$_2$). ^{13}C NMR ($CDCl_3$): δ 216.5 (CO_{cis}), 215.0 (CO_{cis}), 198.7 (CO_{trans}), 198.5 (CO_{trans}), 171.9 (COO), 170.0 (O=C–N), 165.7 (C=N), 155.4 (C on py), 152.8 (C on py), 136.6 (C on py), 127.7 (C on py), 126.6 (C on py), 62.2 (α-*C*H_2), 57.7 (α′-CH), 52.3 (OCH$_3$), 38.0 (β-*C*H_2), 31.0 (CHCH$_3$), 18.9 (CHCH$_3$), 17.9 (CHCH$_3$).

3.5.3. W(CO)$_4$(pyca-GABA-Ala-OEt) (**6**)

Yield: 36%. IR (CH_2Cl_2): 2008 (s), 1898 (vs), 1881 (sh), 1834 (s) 1734 (m), 1669 (m) cm^{-1}. Anal. Calc. for $C_{19}H_{21}N_3O_7W$: C, 38.86; H, 3.60; N, 7.16. Found: C, 38.97; H, 3.96; N, 7.25%. ^{1}H NMR ($CDCl_3$): δ 9.22 (d, $^3J = 5.1$ Hz, 1H, *H* on py), 8.88 (s, 1H, N=C–*H*), 7.93 (m, 1H, *H* on py), 7.87 (d, $^3J = 7.4$ Hz, 1H, *H* on py), 7.83 (m, 1H, *H* on py), 6.25 (d, $^3J = 7.4$ Hz, 1H, O=C–N–*H*), 4.57 (m, 1H, α′-C*H*), 4.27 (m, 2H, α-CH_2), 4.20 (q, $^3J = 7.1$ Hz, CH_2CH$_3$), 2.44 (m, 2H, CH_2), 2.28 (m, 2H, CH_2), 1.43 (d, $^3J = 7.4$ Hz, 3H, CHCH_3), 1.30 (t, $^3J = 7.1$ Hz, 3H, CH$_2$CH_3). ^{13}C NMR ($CDCl_3$): δ 217.1 (CO_{cis}), 215.2 (CO_{cis}), 198.7 (CO_{trans}), 198.5 (CO_{trans}),

173.2 (COO), 171.5 (O=C–N), 164.7 (C=N), 155.6 (C on py), 153.2 (C on py), 136.9 (C on py), 127.6 (C on py), 126.8 (C on py), 66.2 (α-CH_2), 61.7 (OCH_2), 48.4 (α′-CH), 34.2 (CH_2), 32.3 (CH_2), 18.3 ($CHCH_3$), 14.4 (CH_2CH_3).

3.5.4. W(CO)$_4$(pyca-GABA-Val-OMe) (7)

Yield: 42%. IR (CH_2Cl_2): 2017 (s), 1912 (vs), 1886 (sh), 1836 (s), 1745 (m), 1683 (m) cm^{-1}. Anal. Calc. for $C_{20}H_{23}N_3O_7W$: C, 39.95; H, 3.86; N, 6.99. Found: C, 40.06; H, 3.96; N, 7.05%. ^1H NMR ($CDCl_3$): δ 9.23 (d, $^3J = 5.5$ Hz, 1H, *H* on py), 8.86 (s, 1H, N=C–*H*), 7.92 (m, 1H, *H* on py), 7.87 (d, $^3J = 7.8$ Hz, 1H, *H* on py), 7.42 (m, 1H, *H* on py), 6.02 (d, $^3J = 8.5$ Hz, 1H, O=C–N–*H*), 4.55 (dd, $^3J = 8.7$ Hz, $^3J = 5.0$ Hz, 1H, α′-C*H*), 4.25 (m, 2H, α-CH_2), 3.77 (s, 3H, OCH_3), 2.46 (m, 2H, CH_2), 2.29 (m, 2H, CH_2), 2.17 (m, 1H, CH(CH_3)$_2$), 0.95 (d, $^3J = 6.7$ Hz, 3H, CH(CH_3)$_2$), 0.92 (d, $^3J = 6.7$ Hz, 3H, CH(CH_3)$_2$). ^{13}C NMR ($CDCl_3$): δ 217.0 (CO_{cis}), 215.2 (CO_{cis}), 198.7 (CO_{trans}) 198.4 (CO_{trans}), 172.8 (COO), 172.0 (O=C–N), 164.5 (C=N), 155.6 (C on py), 153.1 (C on py), 136.8 (C on py), 127.7 (C on py), 126.8 (C on py), 62.2 (α-CH_2), 57.7 (α′-CH), 52.5 (OCH_3), 32.6 (CH_2), 31.2 ($CHCH_3$), 27.8 (CH_2), 19.2 ($CHCH_3$), 18.0 ($CHCH_3$).

3.6. Synthesis of W(CO)$_4$(pyca-Ala-Ala-OMe) (8)

$W(CO)_4(pip)_2$ (0.500 g, 1.08 mmol), pyridine-2-carboxaldehyde (0.114 g, 1.08 mmol) and H_2N-Ala-Ala-OMe · HCl (0.228 g, 1.08 mmol) were heated to reflux in 20 mL of MeOH creating a deep-purple colored solution. After 1 h of reflux the solvent was removed. Flash chromatography with ethyl acetate as eluant produced a purple band. Solvent was removed and the black product recrystallized from CH_2Cl_2/hexanes.

3.6.1. W(CO)$_4$(pyca-Ala-Ala-OMe) (8)

Yield: 40%. IR (CH_2Cl_2): 2009 (s), 1901 (vs), 1881 (sh), 1831 (s) 1743 (m), 1685 (m) cm^{-1}. Anal. Calc. for $C_{17}H_{17}N_3O_7W \cdot 1/2CH_3CO_2C_2H_5$: C, 37.83; H, 3.51; N, 6.97. Found: C, 37.51; H, 3.48; N, 7.21%. ^1H NMR ($CDCl_3$): δ 9.17 (d, $^3J = 5.2$ Hz, 1H, *H* on py), 9.00 (s, 1H, N=C–*H*), 7.95–7.90 (m, 2H, *H* on py), 7.39 (m, 1H, *H* on py), 6.82 (d, $^3J = 7.2$ Hz, 1H, O=C–N–*H*), 5.08 (q, $^3J = 6.8$ Hz, 1H, α-C*H*), 4.63 (m, 1H, α′-C*H*), 3.78 (s, 3H, OCH_3), 1.75 (d, $^3J = 6.8$ Hz, 3H, α-CHCH_3), 1.53 (d, $^3J = 7.2$ Hz, 3H, α′-CHCH_3). ^{13}C NMR ($CDCl_3$): δ 216.6 (CO_{cis}), 216.1 (CO_{cis}), 198.4 (CO_{trans}), 197.9 (CO_{trans}), 173.0 (COO), 169.0 (O=C–N), 163.3 (C=N), 155.4 (C on py), 152.8 (C on py), 137.1 (C on py), 128.7 (C on py), 127.1 (C on py), 71.7 (α-*C*H), 52.8 (OCH_3), 49.0 (α′-CH), 18.9 (C–CH_3), 18.1 (C–CH_3).

3.7. X-ray structure determination of 5

A single crystal of dimensions 0.2 × 0.1 × 0.03 mm was mounted on a cryoloop using Paraton N-Exxon oil and placed under a stream of cold nitrogen gas. Analyses of the data sets showed negligible decay during data collection. The data were corrected for absorption using the SADABS program. The structures were refined using the Bruker SHELXTL Software Package (Version 6.10) and were solved until the final anisotropic full-matrix, least squares refinement of F^2 converged [30]. Additional experimental details are provided in Table 1.

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Appendix A. Supplementary material

CCDC 299404 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html, or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or e-mail: deposit@ccdc.cam.ac.uk. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jorganchem.2006.10.030.

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