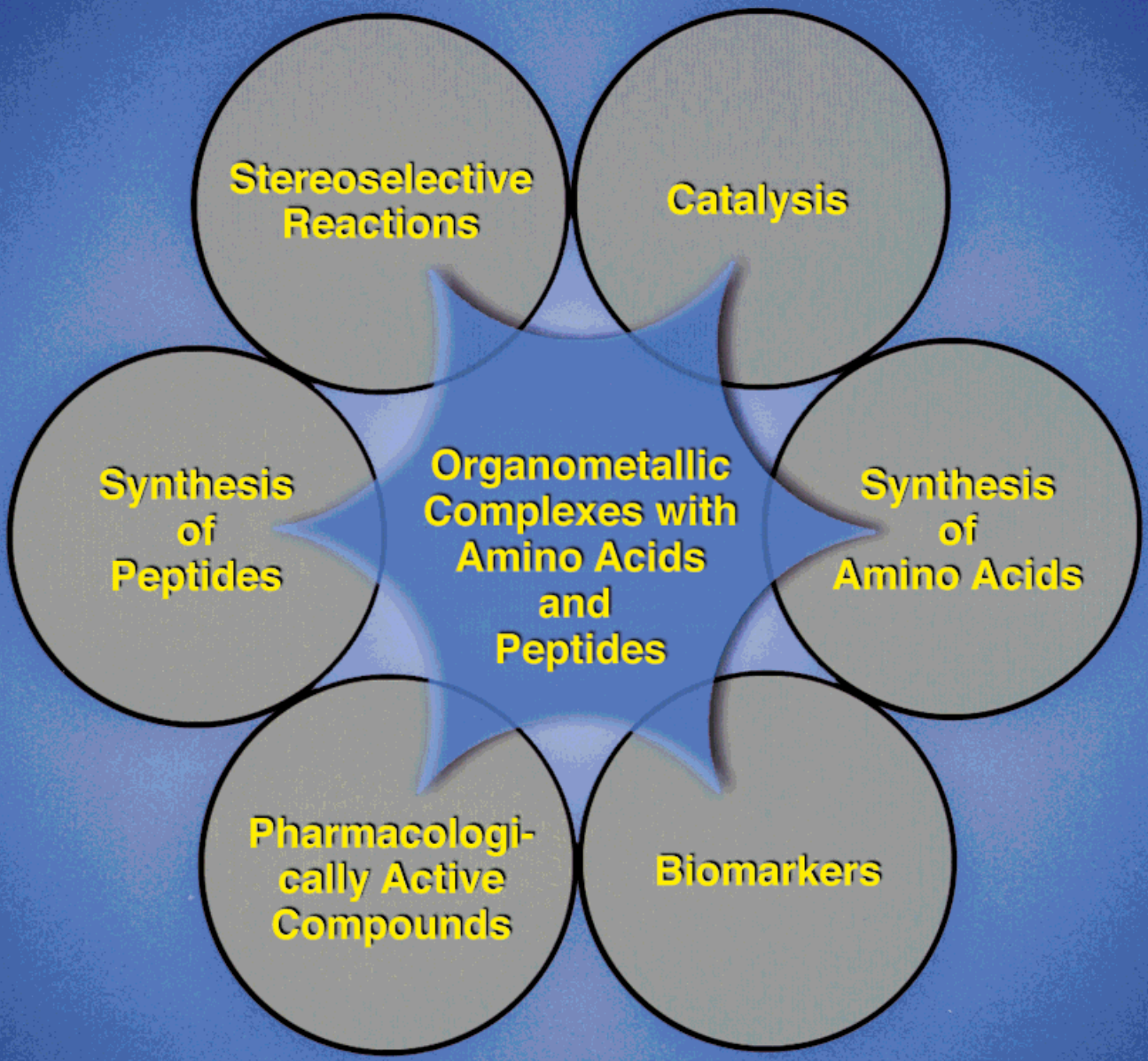

Bioorganometallic Chemistry–Transition Metal Complexes with α-Amino Acids and Peptides**

Kay Severin, Ralph Bergs, and Wolfgang Beck*

Dedicated to Professor Heribert Offermanns on the occasion of his 60th birthday

One of the characteristic developments in the science of the last decade has been the gradual merging of what were once separate research disciplines. Bioorganometallic chemistry is the relatively recent result of such a fusion. Here, organometallic compounds are coupled with biomolecules (sugars, DNA and its constituents, steroids, etc.). The theme of this review article is organometallic complexes of the transition metals with α-amino acids and peptides. This branch of biorganometallic chemistry may be viewed as the logical next step in the classical coordination chemistry of α-amino acid and peptide ligands. On the other hand the special physicochemical properties of these compounds also permit some completely new applications, the potential of interdisciplinary research being reflected in the diversity of these applications: α-amino acids and peptides and their derivatives can not only be synthesized, labeled, and stabilized by organometallic complexes, they can also be activated. This is exploited, for example, in the synthesis of α-amino acids with unusual side chains and has led to the development of an immunoassay based on carbonyl complexes as well as to a template-controlled synthesis of peptides on chiral half-sandwich complexes (synthetic ribosomes). α-Amino acid and peptide ligands also find extended use in enantioselective catalysis. As a consequence of their modular character peptides are of particular interest as ligands for catalyst libraries.

Keywords: α-amino acids · bioorganometallic chemistry · coordination modes · peptides · transition metals

1. Introduction

On the border area between biochemistry and organometallic chemistry a new research field has emerged in recent years: bioorganometallic chemistry. The main features of this new research area are the synthesis, reactions, and applications of organometallic complexes with biogenic ligands. Behind this development a two-way learning process has been underway: on the one hand biologists and biochemists have "discovered" that certain organometallic compounds are stable in the absence of high-purity inert gas atmospheres, often even under physiological conditions, on the other hand, organometallic chemists have recognized the attractiveness and potential of biologically relevant ligands.

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[**] Metal complexes with biologically important ligands, Part 100. Part 99: K. Haas, W. Ponikwar, H. Nöth, W. Beck, *Angew. Chem.* **1998**, *110*, 1200–1203; *Angew. Chem. Int. Ed.* **1998**, *37*, 1086–1089.

This article focuses on organometallic complexes of transition metals with α-amino acids and peptides, a branch of bioorganometallic chemistry.[1] Section 2 gives an overview of the synthesis, structure, and reactivity of the classes of compounds known to date, with the emphasis on α-aminocarboxylate complexes. Compounds with unusual structures and/or patterns of reactivity are discussed, for example α-amino acids with organometallic side chains or protecting groups, macrobicyclic peptide complexes, and pharmacologically active compounds. The following sections deal with the applications of these complexes. The multifaceted character of bioorganometallic chemistry is illustrated here in a series of different themes: α-amino acids and peptide syntheses, stereoselective reactions, immunological assays and other analytical methods, as well as catalytic reactions using α-amino acids and peptides as ligands or as substrates.

2. Synthesis, Structure, and Reactivity

As chiral multifunctional compounds, α-amino acids and peptides are highly versatile ligands in the field of organotransition metal chemistry with its wealth of unusual structures. The compounds described in this section can be divided

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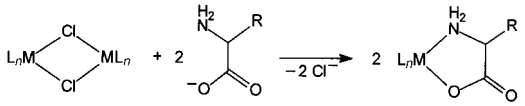
into two classes: A: complexes in which α-amino acids or peptide ligands are coordinated to a suitable organometallic complex fragment through functional group donor atoms (e.g. amino, carboxylato, or sulfanyl groups), and B: complexes in which the amino acid is bound to the metal atom through one (or more) metal–carbon bonds. Compounds belonging to class A show a range of typical coordination modes. With α-amino acid anions N,O-chelates are generally observed. α-Amino acids with coordinating side chains (e.g. cysteine, histidine) can, on the other hand, act as tridentate ligands. The complexation behavior of simple peptides and α-amino acid derivatives is likewise determined by their free functional groups. Amide groups undergo coordination in the presence of strongly Lewis acidic metal centers or on addition of excess base.

Methodologically, classical, *non*-organometallic complex chemistry, that is simple substitution reactions as the primary method of synthesis can be applied. This is especially true for compounds in which the organometallic coligands (Cp* (η^5-C_5Me_5), CO, η^6-arene, etc.) function solely as spectator ligands. Ideal starting compounds for this have proven to be chloro-bridged complexes (Scheme 1). One of the first examples was described by Hieber et al., in which reaction of the chloro-bridged nitrosyl complex $[\{(ON)_2MCl\}_2]$ (M = Fe, Co) with α-aminocarboxylates gave the corresponding N,O-chelate complexes.[2] In some cases, however, the physicochemical idiosyncrasies of the chosen system necessitate and/or facilitate alternative synthetic strategies. This applies in particular to complexes in which the organometallic fragment is anchored to the amino acid side chain through σ or π coordination (see Section 2.4) and to complexes such as the hydrido phosphane complex **19**, formed by the oxidative addition of α-amino acids to $[Ru(CO)_3(PPh_3)_2]$ (see Section 2.1).



Scheme 1. Synthesis of N,O-chelates by reaction of chloro-bridged complexes with α-amino acid ions

2.1. Carbonyl Complexes

The first evidence of an α-aminocarboxylate carbonyl complex—$[Fe(CysO)_2(CO)_2]$—was obtained as long ago as 1929.[3a] Four years later the precise synthesis of the compound was reported;[3b] this was the first isolated and characterized organometallic α-amino acid complex. On the basis of IR spectroscopic data an N,S-chelate with *cis*-oriented carbonyl ligands was proposed.[4] Interestingly, the active

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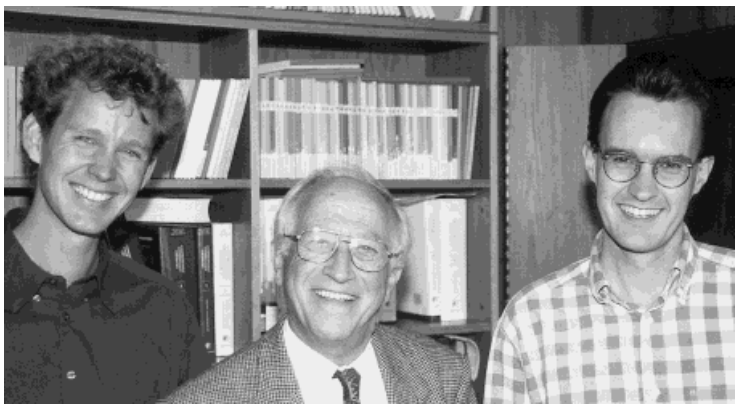

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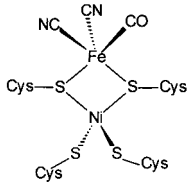
center of Ni/Fe hydrogenases has likewise recently been shown to contain an iron carbonyl complex (**1**).[5]



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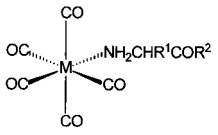
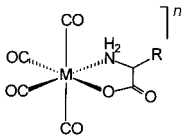
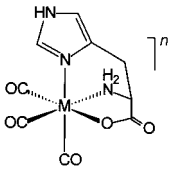


	M
2	Cr
3	W



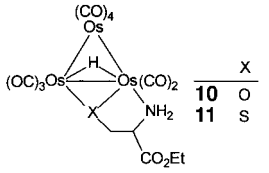
	M	*n*
4	W	−1
5	Re	0



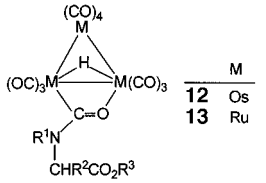
	M	*n*
6	Cr	−1
7	Mo	−1
8	W	−1
9	Mn	0

Today numerous α-aminocarboxylate carbonyl complexes are known, among them complexes of Cr, Mo, W, Mn, Re, Fe, Ru, Os, and Rh.[6] The photochemical reaction of $[Cr(CO)_6]$ or $[W(CO)_6]$ with α-amino acid or peptide esters leads to the η^1-amine complexes **2** and **3**,[7] which are relatively unstable in solution. By contrast, the reaction of $[W(CO)_5(thf)]$ with alkali metal α-aminocarboxylates affords the N,O-chelate **4**,[8] which exhibits intermolecular hydrogen bonding in the crystal between the amine protons and neighboring carboxylate groups. The corresponding neutral Re N,O-chelate **5** is synthesized from the organometallic Lewis acid $[Re(CO)_4(OEt_2)]BF_4$.[9] Tricarbonyl complexes of type **6**–**9** are obtained with the tridentate ligands L-histidinate and L-cysteine.[10] The spatial orientation of the donor atoms is fixed here by the configuration at the α-C atom, which means that coordination to the $M(CO)_3$ group is stereospecific. In its complexation behavior the tridentate histidinate ligand can be likened to the hydridotrispyrazolylborate (Tp) and cyclopentadienide (Cp) ions: by analogy with $[TpM(CO)_3]$ and $[CpM(CO)_3]$ (M = Mo, W), **6** and **7** react with electrophiles with substitution of a CO ligand.[10b] Water-soluble tricarbonyldiiminorhenium(I) complexes with histidine ligands have recently been proposed as sensitizers for photochemically induced electron-transfer processes.[11] Other $Re(CO)_n$ complexes with α-amino acids and peptides are accessible by reaction with $[Re(CO)_5Br]$,[12] many of which exhibit unusual η^1-NH_2 coordination with the free acid group.

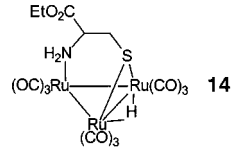
Rare coordination modes are also observed in reactions with metal carbonyl clusters: depending on the reaction conditions the reaction of trinuclear osmium carbonyl clusters with α-amino acid esters can lead either to the alkoxide- and thiolate-bridged complexes **10** and **11** or to carbamoyl hydride complexes of type **12**.[13] Reaction with $[Ru_3(CO)_{12}]$ affords the structural analogues **13** and **14**.[14] Chiral heterotrinuclear hydrido clusters of type $[(\mu\text{-RC})CoM^1M^2Cp(CO)_8H]$ (R = Me, Ph; M^1 = Ru, Os; M^2 = Mo, W) react with the prochiral alanine precursor methyl acetamidoacrylate with insertion into the M–H function and substitution of a CO ligand (**15**–**18**).[15] Metalation occurs regioselectively at the α-C atom and is diastereospecific. The CoRuMo compound **15** is the first



	X
10	O
11	S



	M
12	Os
13	Ru



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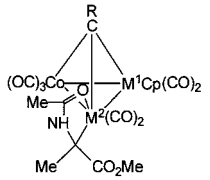
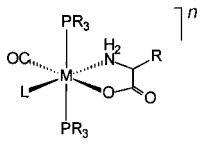


	M^1	M^2
15	Mo	Ru
16	W	Ru
17	Mo	Os
18	W	Os

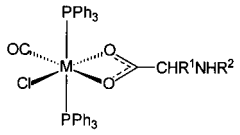
fully characterized key intermediate in the enantioselective catalytic hydrogenation of amidoacrylic acid derivatives (other α-metalated amino acid derivatives are described in Section 2.4). Such a hydrogenation is the key reaction in the industrial synthesis of L-dopa from the corresponding dehydroamino acid.

The functionalization of electron-rich, phosphane-substituted carbonyl complexes of the late transition metals with chiral α-aminocarboxylate ligands is of particular interest in its catalytic applications (see Section 6), research to date having focused on octahedral Ru^{II} and Os^{II} and square-planar Rh^{I} complexes.

The reaction of $[MHCl(CO)(PPh_3)_3]$[16] or $[MHCl(CO)(PMe_tBu_2)_2]$ (M = Ru, Os)[17] with α-amino acid anions generates the hydrido complexes **19** and **20** and **21** and **22**, respectively.[18] The dicarbonyl complexes **23** are accessible



	M	PR_3	L	*n*
19	Ru	PPh_3	H	0
20	Os	PPh_3	H	0
21	Ru	PMe_tBu_2	H	0
22	Os	PMe_tBu_2	H	0
23	Ru	PPh_3	CO	+1



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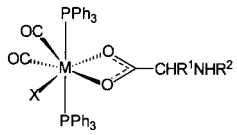


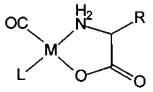
	M	X
25	Mo	Br
26	W	Br
27	Mo	$O_2CCHR^1NHR^2$

from the organometallic Lewis acid $[Ru(CO)_2(PPh_3)_2](BF_4)_2$. Compounds of type **19** can, alternatively, be obtained through the oxidative addition of α-amino acids to $[Ru(CO)_3(PPh_3)_2]$,[16] in an example of a reaction type described only very rarely to date. In the absence of base, reaction of $[RuHCl(CO)(PPh_3)_3]$ with α-amino acids leads to evolution of hydrogen and the formation of the chloro complexes $[RuCl(NH_2CHRCO_2)(CO)(PPh_3)_2]$, which are unusual in that the two phosphane ligands adopt an unexpected *cis* orientation.

In general, the complexation behavior of *N*-acyl amino acids corresponds to that of simple carboxylic acids; depending on the Lewis acid character of the metal atom this can result in mono- or bidentate coordination of the carboxylate

group. Whereas η^2 coordination is observed for the Ru^{II}, Mo^{II}, and W^{II} complexes **24**–**26**, the Mo^{II} complex **27** contains both η^1- *and* η^2-coordinated ligands.[20]

Square-planar α-aminocarboxylate carbonyl complexes are known for rhodium(I) (**28**, **29**)[21] and platinum(II) (**30**).[22] Dicarbonyl Rh^I complexes of formula

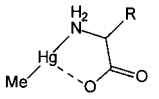


	M	L
28	Rh	CO
29	Rh	PPh_3
30	Pt	Cl

$[Rh(CO)_2(NH_2CHRCO_2)]$ (**28**) were described for the first time in 1976.[21g] In a subsequent study, however, these compounds were shown to be HCl adducts,[21c] which exist presumably as oligomers; this study also described an alternative synthetic route to **28**.[21c] An analogous L-aziridine-2-carboxylate complex has recently been characterized crystallographically.[21b] Rhodium(I) phosphane complexes of type **29** were obtained by the reaction of the cationic complex $[Rh(CH_3CN)(CO)(PPh_3)_2]BF_4$ with L-alaninate or L-phenylalaninate.[21a] In the crystalline state these compounds exhibit an interesting superstructure with intermolecular hydrogen bonding (as also seen in **3**[8]).

2.2. η^1-Alkyl, η^2-Olefin, and η^3-Allyl Complexes

The extremely toxic $MeHg^+$ ion is formed in the organism by biomethylation of Hg^{2+}. From a physiological point of view the interaction of $MeHg^+$ with α-amino acids and peptides is interesting because complexation can strongly influence the bioavailability of this heavy metal compound. In addition to numerous studies of their behavior in solution,[23] α-aminocarboxylate complexes of formula $[MeHg(NH_2CHRCO_2)]$ (**31**)[24] and the dipeptide complex [MeHg(GlyGlyO)][25] have been isolated and characterized as model compounds. As can



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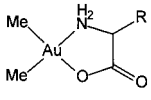

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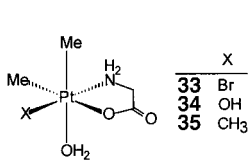
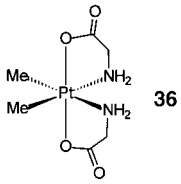
be seen from X-ray crystal structure analyses, in these complexes the $MeHg^+$ ion is coordinated in a linear fashion to the amino or thiol group. In the crystal intra- and intermolecular interactions are also discernible between the Hg atom and the carboxylate O atoms. Monomeric, light-sensitive dimethylgold(III) complexes (**32**) are obtained by the reaction of $[(H_3C)_2Au(OH_2)]NO_3$ with α-amino acid salts.[26] With the exception of $[(H_3C)_2Au(CysO)]$, N,O-chelates are observed. An S,O-chelate structure has been proposed for $[(H_3C)_2Au(CysO)]$.

Owing to the pharmacological importance of cisplatin, studies of the chemistry of platinum amino acid complexes have mostly focused on non-organometallic compounds of oxidation state +II.[27] The exception are octahedral di- and trimethyl Pt^{IV} complexes, whose synthesis and reactivity have been intensively investigated in recent years.[28] In aqueous solution these chelate complexes are present as a series of stereoisomers, differing in the orientation of the α-amino acid carboxylate ligands relative to the methyl ligands which are locked into a *cis* configuration. The glycinate complexes **33**–**36** serve as representatives of this class. Chelate complexes with Pd–aryl bonds of type $[(tol_3P)(\eta^1\text{-aryl})Pd(NH_2CHRCO_2)]$ are formed from the chloro-bridged complex $[\{(tol_3P)(\eta^1\text{-aryl})PdCl\}_2]$ by reaction with α-aminocarboxylates.[29]

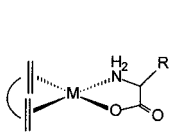


	X
33	Br
34	OH
35	CH_3

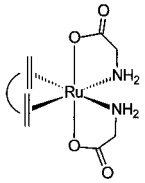


36

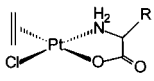
The reaction of the chloro-bridged complex $[\{(cod)MCl\}_2]$ (M = Rh, Ir; cod = 1,5-cyclooctadiene) with glycinate and prolinate was first reported in 1975,[30] and affords the N,O-chelates **37** and **38**. The same study also described complexes



	M	Diene
37	Rh	cod
38	Ir	cod



	Diene
39	cod
40	nbd



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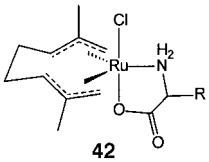
of formula $[(diene)Ru(GlyO)_2]\cdot x\,H_2O$ (diene = norbornadiene, nbd, cod) (**39**, **40**), formed from the reaction of polymeric $[\{(diene)RuCl_2\}_n]$ with glycinate. The reaction of $[\{(diene)RuCl_2\}_n]$ with α-amino acids has since been extensively investigated by Sheldrick et al.[31] Insoluble complexes of formula $[\{(diene)RuCl(NH_2CHRCO_2)\}_n]$ are formed in methanol, whereas reaction in water affords the known complexes **39** and **40**. IR spectroscopic data indicate that the α-amino acid anions function in these polymeric compounds as tridentate ligands with bridging carboxylate groups. This comparatively unusual mode of coordination was confirmed for the tetrameric complex $[\{(cod)RuCl(D,L\text{-PheO})\}_4]$ by an X-ray crystal structure analysis.[31c] Reaction with histidinate or with the anions of sulfur-containing α-amino acids yields compounds in which the α-aminocarboxylate anions are present as bi-, tri-, or tetradentate ligands with S,N-, S,N,O-, N,N,O-, and S,S,N,O-coordination.[31a, b]

Among the best studied α-aminocarboxylate olefin complexes are Pt(II) complexes of general formula $[PtCl(NH_2CHRCO_2)(olefin)]$ (**41**).[22, 32] These compounds are known to exist in two stable isomeric forms: *trans*-(*N*,olefin) and *cis*-(*N*,olefin). However, depending on the reaction sequence chosen—making use of the differing *trans*-effects of ethylene and chloride as ligands—either isomer can be synthesized selectively: reaction of Zeise's salt with α-amino acid anions generates the *trans*-(*N*,olefin) isomer, whereas substitution of a chloride ligand in $[PtCl_3(NH_2CHRCO_2H)]^-$ with ethylene and subsequent elimination of HCl gives the thermodynamically favored *cis*-(*N*,olefin) isomer. The diastereoselectivity of the coordination

of prochiral olefins has been systematically investigated.[33] For *trans*-(*N*,olefin) complexes selectivity is low. For *cis*-(*N*,olefin) complexes on the other hand, particularly with *N*-alkyl amino acids such as sarcosine or proline and functionalized olefins, remarkable selectivities are observed in some cases; this is attributed to the selective stabilization of one isomer by intramolecular hydrogen bonding.

The complex $[\{(\eta^3{:}\eta^3\text{-}C_{10}H_{16})RuCl_2\}_2]$ is unusual for two reasons: on the one hand the Ru atom is in the formal oxidation state +IV, and on the other the $(\eta^3{:}\eta^3\text{-}C_{10}H_{16})Ru$ fragment is chiral. Its reaction with salts of α-amino acids results in the neutral, trigonal-bipyramidal Ru^{IV} complexes **42**.[34] Use of α-amino acid esters with coordinating side chains



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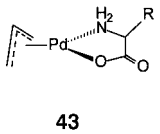
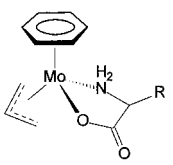


43

led to the isolation of a cationic chelate complex with N,S-coordination (L-CysOMe) and a dinuclear complex with an N,N-bridging ester (L-HisOMe). Allyl complexes of Pd^{II} with α-aminocarboxylate ligands (**43**) have been known for some time already.[21b, 35] Such complexes can be prepared from $[\{(\eta^3\text{-allyl})PdCl\}_2]$ and show dynamic behavior in solution. Complexes of similar structure are proposed as intermediates in the asymmetric α-allylation of carbonyl compounds.[36]

2.3. η^5-Cyclopentadienyl and η^6-Arene Complexes

The first half-sandwich complex with an α-aminocarboxylate ligand, a η^6-benzene, η^3-allyl complex **44**, was synthesized in 1973.[37] Since then, a large number of such com-



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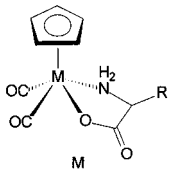
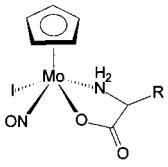


	M
45	Mo
46	W

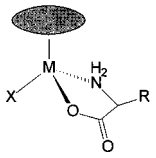


47

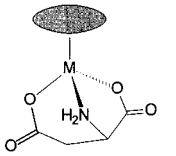
pounds have been characterized. Although certain coordination modes predominate, these complexes exhibit the structural diversity seen with ambidentate α-amino acid and peptides ligands. A particularly interesting feature of these compounds is their stereochemistry, the metal atom functioning here as an additional chiral center, opening up new horizons in stereoselective reactions.

Chiral α-aminocarboxylate complexes of Mo and W (**45**, **46**) have been obtained by the reaction of $[CpM(CO)_3Cl]$ (M = Mo, W) with the alkali metal salts of various α-amino acids.[35a, 38] Replacement of the two carbonyl ligands in **45** with a nitrosyl and an iodide ligand affords the isoelectronic derivatives $[CpMoI(NO)(NH_2CHRCO_2)]$ (**47**). This complex can be synthesized from $[\{CpMo(NO)I_2\}_2]$; corresponding Cp* complexes were prepared from $[\{Cp^*Mo(NO)I_2\}_2]$.[39] Complexes **45**–**47** have four-legged piano-stool geometry. If the α-aminocarboxylate used is optically active, four diastereoisomers are possible for **47**. During the synthesis aor upon workup, one isomer is substantially enriched. For the glycinate complex $[CpMoI(NO)(NH_2CH_2RCO_2)]$ the *cis* and *trans* isomers are obtained in a 7:3 ratio.

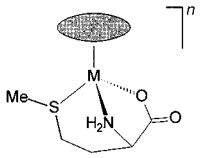
η^5-Cyclopentadienyl complexes of the elements Co, Rh, Ir, and Ru and η^6-arene complexes of Ru and Os show great similarities in their structure and reactivity. These complexes are generally prepared by the reaction of α-aminocarboxylates or α-amino acid N-glycosides[32a] with the halogen-bridged complexes $[\{Cp^*MX_2\}_2]$ (M = Co, Rh, Ir, Ru; X = Cl, I),[21b, 32a, 35a, 40] $[\{\eta^6\text{-arene})RuCl_2\}_2]$ (arene = C_6H_6, C_6Me_6, mesitylene, *p*-cymene),[35a, 40g, 41] $[Cp^*Co(\mu\text{-}Cl)_3CoCp^*]^+$,[42] or $[Cp^*Co(CO)I_2]$.[43] Simple α-amino acid anions yield the diastereoisomeric N,O-chelates **48**–**50**, usually in a 1:1 ratio.



	M	π-Donor	X
48	Co	Cp^*	I
49	Rh	Cp^*	Cl
50	Ir	Cp^*	Cl
51	Ru	C_6H_6	Cl
52	Ru	cymene	Cl
53	Ru	Mes	Cl
54	Ru^-	Cp^*	Cl
55	Os^+	C_6H_6	PR_3



	M	π-Donor
56	Co	Cp^*
57	Rh	Cp^*
58	Ir	Cp^*



	M	π-Donor	*n*
59	Co	Cp^*	+1
60	Rh	Cp^*	+1
61	Ir	Cp^*	+1
62	Ru	Cp^*	0

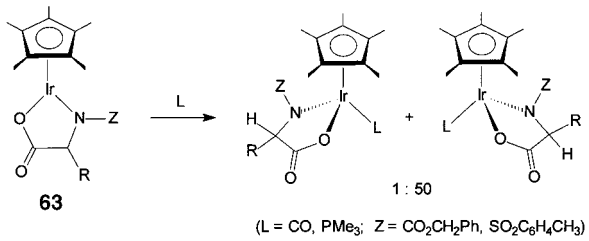
By contrast, high selectivity is observed with *N*-alkylated α-aminocarboxylates such as prolinate (11:1)[40f, g] or *N,N*-dimethylvalinate (over 50:1).[40b] At ambient temperature the Ru, Rh, and Ir complexes are configurationally stable, but at higher temperatures in solution these complexes undergo epimerization at the metal center. This phenomenon is observed even at room temperature for some Co complexes. The metal–halogen bond in **48**–**54** is relatively labile; substitution reactions allow the introduction of triphenylphosphane[40f] or alkyne ligands.[40d] For **49**, abstraction of the chloride ligand with $AgBF_4$ results in the formation of a trinuclear complex with bridging carboxylate groups. Interestingly, this trimerization proceeds with chiral self-recognition, that is the $S_C,S_C,S_C,S_{Rh},S_{Rh},S_{Rh}$ isomer is formed with high selectivity.[44a, b] A similar trinuclear carboxylate-bridged iridium complex, $[\{Cp^*Ir(prolinate)\}_3]^{3+}$, was recently obtained from $[Cp^*IrCl(prolinate)]$ and $AgOSO_2CF_3$.[44c]

A trinuclear deoxyadenosine-bridged Cp*Rh complex is able to act as a host for amino acids.[44d, e]

α-Amino acids with coordinating side chains can function as tridentate ligands, leading to the formation of N,O,N-(histidine[40g, 42]), N,O,O- (asparagine,[43] aspartic acid[40g, 42, 43]) (**56**–**58**) and N,O,S-chelates (methionine,[32a, 40c, 42], penicillamine[42]) (**59**–**62**). A point of note is the structure of the Cp*Co asparaginate complexes **56**: these compounds cocrys-

tallize with alkali metal halides; the asparagine dianion is capable of functioning as an up to octadentate ligand.[42, 43] The phosphane-substituted η^6-arene Os^{II} complexes $[(C_6H_6)Os(NH_2CHRCO_2)(PR_3)]X$ (**55**) ($PR_3 = PiPr_3$, $PMetBu_2$; X = I, SbF_6, PF_6) have been synthesized from $[(C_6H_6)Os(PR_3)I_2]$.[17] Surprisingly, unlike with the complexes **48**–**54**, this reaction proceeds stereospecifically. The hydridotrispyrazolylborato Rh^{III} complexes $[TpRhCl(NH_2CHRCO_2)]$ and $[Tp^*RhCl(NH_2CHRCO_2)]$ (Tp^* = hydridotris-3,5-dimethylpyrazolylborate) are obtained, by analogy with **49,** from the chloro-bridged complexes $[\{TpRhCl_2\}_2]$ and $[\{Tp^*RhCl_2\}_2]$[45]

Dianions of N-functionalized α-amino acids permit the stabilization of the electronically unsaturated 16-electron Cp^*Ir^{III} complexes **63**.[46a–c] These compounds add CO or sterically undemanding phosphanes such as PMe_3 or PMe_2Ph with remarkable diastereoselectivities of over 50:1 (Scheme 2). On addition of a chiral amine, the ^1H NMR spectrum of the adduct formed can be used to determine the

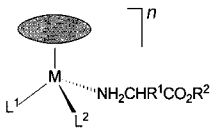


63

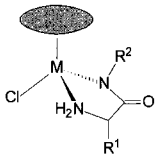
Scheme 2. Stereoselective addition of ligands to unsaturated $[Cp^*Ir^{III}]$ complexes.

enantiomeric purity of the amine used.[46a] Analogous Rh^{III} complexes achieve electronic saturation through dimerization.[44b] Cp*Ru complexes of prolinate and methioninate were employed for the stereoselective synthesis of planar chiral ruthenocenes.[46d]

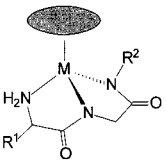
In our research group we have developed an iterative, sequence-specific peptide synthesis using half-sandwich complexes (see Section 4).[47] In the course of this work we have obtained detailed information about the coordination behavior of α-amino acid esters, α-amino acid amides,[48d] and di- and oligopeptides.[47, 48] α-Amino acid or peptide esters form cationic N,O-chelates or η^1-amine complexes (**64**–**70**), though in some cases the two forms exist in equilibrium with one another. The coordination of the ester carbonyl group is favored in polar solvents such as methanol and can be forced by abstraction of a halide ligand with silver salts. If the synthesis is carried out in the presence of an additional equivalent of base, the chiral (N^{amine},N^{amide})-chelate complexes **71**–**74** are obtained. Although these compounds with chiral peptide ester ligands are present as a mixture of two diastereoisomers, at ambient temperature the ^1H NMR spectrum in CD_3OD shows only one, averaged, set of signals, indicating rapid inversion at the metal atom. With dianions of tripeptide esters the N,N′,N″-chelates **75**, **76** are isolated. The Ru complexes **76** are formed with very high diastereoselectivity. As shown by an X-ray crystal structure analysis, this mode of coordination causes an unusual pyramidalization of the bridgehead amide N atom.



	M	L^1	L^2	n	π-Donor
64	Co	I	I	0	Cp
65	Rh	Cl	Cl	0	Cp*
66	Ir	Cl	Cl	0	Cp*
67	Ru	PPh_3	PPh_3	+1	Cp
68	Ru	PPh_3	CO	+1	Cp
69	Ru	Cl	Cl	0	Cp
70	Cr	Br	Br	0	Cp*

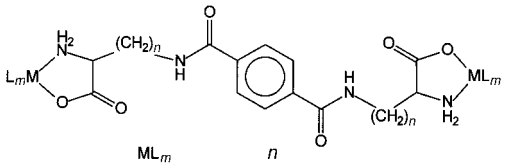


	M	π-Donor
71	Rh	Cp*
72	Ir	Cp*
73	Ru	C_6Me_6
74	Ru	cymene



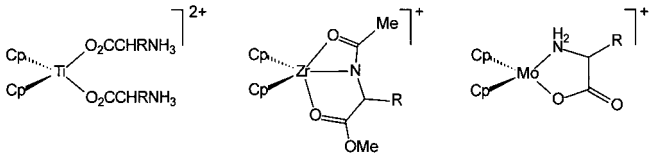
	M	π-Donor
75	Rh	Cp*
76	Ru	C_6Me_6

Coordination of diaminocarboxylic acids (e.g. lysine) to Cu^{2+} leads to the formation of N,O-chelates bearing a free amino group, which can be selectively functionalized through reaction with electrophiles and subsequent demetalation.[49] This reaction sequence also allows the synthesis of terephthalamide-bridged α,γ-, α,δ-, and α,ε-diaminocarboxylic acids.[49b] Reaction of these bridged amino acids with chloro-bridged half-sandwich complexes yields—by analogy with **49**–**52**—compounds **77**–**80**, as a mixture of two diastereoisomers.[50]



	ML_m	n
77	[Cp*RhCl]	2 - 4
78	[Cp*IrCl]	2 - 4
79	$[(C_6Me_6)RuCl]$	2 - 4
80	[(cymene)RuCl]	2 - 4

Bis(cyclopentadienyl) complexes of the early transition metals, titanocene dichloride in particular, attract considerable interest on account of their cytostatic activity. The Ti^{IV} complexes **81** were synthesized and characterized as model compounds for interactions with biologically relevant ligands.[51] In the crystal these complexes show η^1 coordination



81 **82** **83**

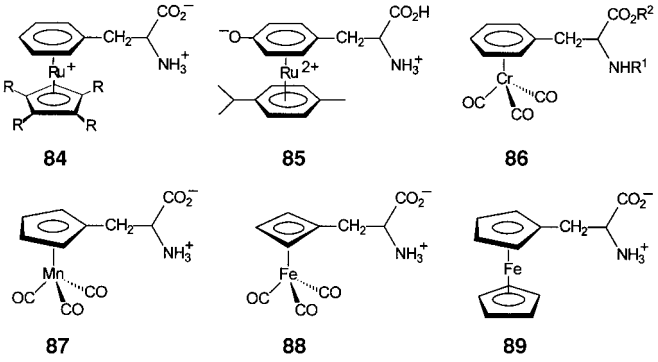
of the carboxylate group along with free, protonated amino groups. In vivo studies have shown that the α-aminocarboxylate complexes **81** also possess antitumor activity.[52] Unlike $[Cp_2TiCl_2]$, $[Cp_2NbCl_2]$ shows no discernible interaction with α-amino acids in aqueous solution.[53] Analogues of **81** of formula $[Cp_2Ti(O_2CCHR^1NHCOR^2)_2]$ are obtained by reaction of titanocene dichloride with *N*-acyl α-amino acids.[35a, 54] These complexes can be used as acylation reagents (see Sec-

tion 4).[54a] The coordination of C,N-protected α-amino acids and peptides to $ZrCp_2$ fragments is achieved by reaction of $[Cp_2ZrMe(thf)]^+$ with $OCNCHR^1COR^2$ (**82**).[55] Cationic compounds of formula $[Cp_2Mo(NH_2CHRCO_2)]X$ ($X = Cl$, PF_6) (**83**) were synthesized some time ago from $[Cp_2MoCl_2]$.[56]

2.4. α-Amino Acids and Peptides with Organometallic Side Chains

Replacing α-amino acids with synthetic, non-coded analogues is an effective way of selectively influencing the physical, chemical, and biological properties of peptides. The coordination of organometallic complex fragments to α-amino acid side chains is doubly interesting in this context: not only do the special properties of such α-amino acids (relatively hydrophobic, aromatic character in some cases, unconventional shapes) offer a means of probing the stereoelectronic prerequisites for specific substrate – receptor interactions, the spectroscopic properties of the complex fragments allow them to be used as biomarkers (see Section 5). Moreover, the possibility of extensive functionalization means that α-amino acids with organometallic side chains are also interesting from a synthetic viewpoint (see Section 3).

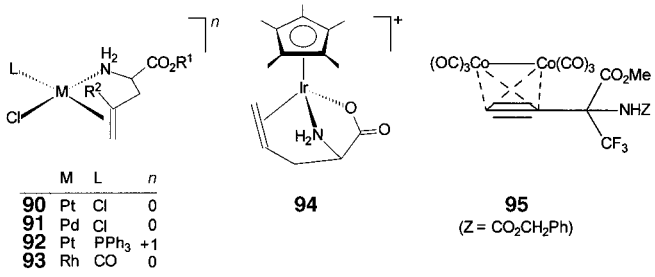
The π-electron system of aromatic α-amino acid side chains is an obvious target for the introduction of transition metal complex fragments. Starting with $[(\eta^5\text{-}C_5R_5)Ru(CH_3CN)_3]^+$ or $[(\eta^5\text{-}C_5R_5)RuCl_2]_2$ ($R = Me$, H), it is possible to synthesize $[(\eta^5\text{-}C_5R_5)Ru(\eta^6\text{-arene})]$ sandwich complexes with derivatives of phenylalanine (**84**), tryptophan, and tyrosine.[40c, 57] The $(\eta^5\text{-}C_5R_5)Ru$ fragment can also be replaced by $(\eta^6$-cymene)Ru, as in **85**.[58] The analogous chromium tricarbonyl



complexes **86** were first obtained by reaction with $[Cr(CO)_6]$.[59] Carbonyl complexes of the elements Fe and Mn are accessible by the metal-mediated synthesis (and stabilization) of the unnatural amino acids cyclopentadienylalanine and cyclobutadienylalanine (**87**, **88**).[60] The synthesis of the ferrocene-containing α-amino acids D,L-β-ferrocenylalanine **89** and D,L-*p*-ferrocenylphenylalanine was reported as long ago as 1957 by Schlögl.[61] The following period saw the introduction of alternative synthetic pathways,[62] including a synthesis of ferrocenylbis(alanine).[63] Optically active **89** was obtained by asymmetric hydrogenation of dehydro-*N*-acyl-amino acids with Rh phosphane catalysts[64] and by enzymatic resolution of the racemate.[65]

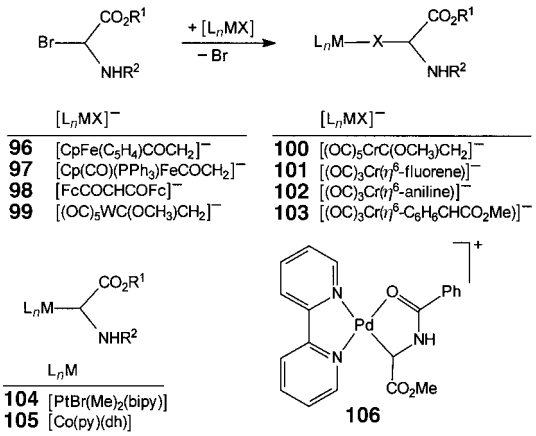
Crucial to the use of organometallic amino acids in biochemical investigations is the possibility of incorporating these compounds into peptides. A Cp*Ru complex of type **84** was used to synthesize dipeptides by the carbodiimide method,[57a] though the sensitivity to hydrolysis of Cp*Ru sandwich complexes imposes limitations on more extensive use. By contrast, cymantrenyl- and ferrocenylalanine have proven to be particularly stable, allowing even solid-phase peptide syntheses to be carried out (cleavage of the peptide from the resin with HF!).[66] This was used to synthesize organometallic derivatives of a series of biologically active peptides (e.g. encephalins).[66b–e] The cymantrenyl compounds are remarkably versatile; photochemical substitution reactions permit the exchange of CO for phosphane ligands,[66a, b] enabling the size and hydrophobic character of these α-amino acids–and corresponding peptides—to be varied selectively.

With the use of synthetic amino acids such as *C*-allyl- or *C*-alkynylglycine, π coordination to organometallic fragments is likewise possible. Chloro-bridged complexes of the elements Ir, Pd, and Pt can be used to obtain the chelate complexes **90** – **94** by reaction with *C*-allylglycine or *C*-allylglycine esters.[67] By analogy with allylamines, the coordinated olefin in the



cationic compound **92** reacts with C-nucleophiles with C – C coupling to form γ-metalated amino acid esters,[67a] which can then be demetalated. Interesting further chemistry is also shown by the Rh complex **93**: reaction with HCl and $P(OMe)_3$ generates *N*-acyl complexes by hydrometalation and insertion of CO. After cleavage of the ligand, γ-lactams were obtained.[68] *C*-Vinylglycinate can be stabilized as an N,O-chelate coordinated to a [Cp*(Cl)M] fragment ($M = Rh$, Ir).[67a] Reaction of the alkynyltrifluoromethyl α-amino acid $ZNHC(CF_3)(C{\equiv}CH)CO_2Me$ ($Z = CO_2CH_2Ph$) with $[Co_2(CO)_8]$ resulted in the formation of the metallatetrahedrane **95**.[69] Complex **95** reacts with norbornene in a $[2+2+1]$ cycloaddition to give a cyclopentenone-substituted α-trifluoromethyl amino acid derivative.

α-Bromoglycine derivatives ("electrophilic glycine equivalents") are valuable building blocks for the synthesis of α-amino acids with modified side chains. Reaction with base generates acylimines, which are not isolated, but are allowed to react in situ with nucleophiles such as amines, thiols, silyl enol ethers, Lipshutz cuprates, or Grignard reagents.[70] Transition metal fragments can be introduced in analogous manner by reaction of methyl α-bromohippurate with organometallic C- and N-nucleophiles (Scheme 3).[71] Nucleophiles that have been used include acetylferrocene enolates

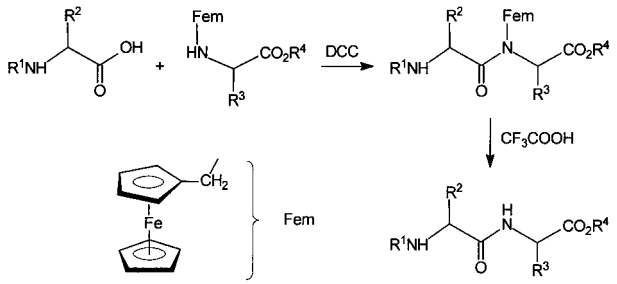


Scheme 3. Synthesis of α-amino acids with organometallic side chains by reaction of electrophilic glycine equivalents with nucleophilic transition metal complexes.

(**96**), $[CpFe(CO)(PPh_3)(COCH_3)]$ (**97**), and a ferrocene-containing acetylacetonate derivative (**98**), as well as anions of Fischer carbene complexes (**99**, **100**) and arenechromium tricarbonyl complexes (**101**, **102**). Analogous chromium complexes had previously been obtained from chlorinated glycine derivatives (**103**) or iodinated alanine derivatives.[72] Nucleophilic attack can also occur through the metal atom directly: reaction of methyl α-bromohippurate with $[PtMe_2(bipy)]$ or with $[Co(py)(dh)]^-$ (bipy = 2,2′-bipyridine, py = pyridine, dh = dimethylglyoxime) affords the complexes **104** and **105**,[73] which were among the first examples of α-transition metalated amino acid derivatives. The cationic C,O-chelate complex **106** can be obtained by reaction of $[Pd(dba)_2]$ (dba = dibenzylideneacetone) with methyl α-bromohippurate in the presence of bipyridyl, followed by abstraction of halide with silver salts.[73b] The oxidative addition of a N-protected asparatic acid anhydride to a Ni^0 complex gives a chiral metallacycle, which can be used for the synthesis of α-amino acids.[73c]

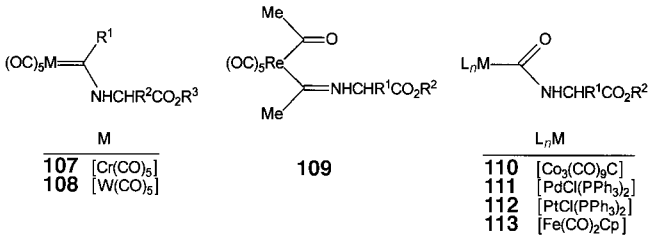
2.5. α-Amino Acids and Peptides with Organometallic Protecting Groups

The selective fine-tuning of the solubility and secondary structure of peptides is of great synthetic utility. Use of the chromophoric and lipophilic ferrocenylmethyl residue (Fem)[74] permits the simple and reversible masking of peptide bonds.[75] The Fem group can be introduced without racemization by catalytic reductive alkylation of α-amino acids or α-amino acid esters with ferrocenecarboxaldehyde and hydrogen. The resulting *N*-Fem α-amino acid derivatives can then undergo coupling reactions by the carbodiimide method (Scheme 4). In addition to their strongly lipophilic character, Fem-masked peptides have one further advantage: they are colored (yellow), which simplifies their chromatographic purification. Instead of the ferrocenylmethyl residue, the $[(\eta^4\text{-}RC_6H_6)Fe(CO)_3]$ group can be introduced under mild conditions (cf. Section 5).[76] Following any subsequent transformations the complex can then be recovered almost quantitatively through cleavage with trifluoroacetic acid.



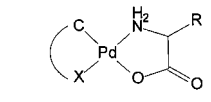
Scheme 4. Reversible masking of peptide bonds with the lipophilic and colored ferrocenylmethyl (Fem) residue. DCC = dicyclohexylcarbodiimide.

A number of carbonyl complexes have been proposed as amino protecting groups for use in peptide synthesis. Examples include the aminocarbene complexes **107** and **108** formed by the aminolysis of $[(OC)_5M{=}CR(OCH_3)]$ (M = Cr, W) with α-amino acid esters.[77] Another organometallic amino protecting group is based on a carbonylrhenium complex: here α-amino acid esters are condensed with Re acetylacetonate complexes to give the rhena-β-ketoimine derivatives **109** as a mixture of two isomers.[78] α-Amino acid or peptide esters can be functionalized with a cobalt carbonyl cluster by reaction with $[(OC)_9Co_3CCO]PF_6$ (**110**).[79] Analogous carbamoyl complexes are formed by the reaction of $[(Ph_3P)_2MCl_2]$ (M = Pd, Pt) with CO in the presence of α-amino acid esters (**111**, **112**)[80] and by the reaction of $[CpFe(CO)_3]CF_3SO_3$ with α-amino acid esters (**113**).[8a] α-Amino acid esters can also be added to coordinated olefins.[81b]



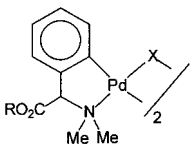
2.6. Other Compounds

Cyclopalladated chloro-bridged complexes of type $[(C\,\widehat{N})Pd(\mu\text{-}Cl)]_2$ (also planar chiral ferrocene derivatives) and the corresponding acetylacetonate derivatives have proven suitable starting compounds for the synthesis of square-planar α-aminocarboxylate complexes (**114**–**120**).[21b, 32a, 35, 82] In these compounds the carboxylate group is generally oriented *trans* to the metalated C atom. Complexes with chiral cyclometalated ligands (**118**–**120**) merit particular attention.[83a,d] In their reactions with α-amino acids, the



products formed are diastereomeric. Integration of the corresponding ^{1}H NMR signals allows the enantiomeric ratio of the α-amino acid used to be determined.[84] If racemic cyclometalated ligands are used (**120**), they can then be obtained in optically active form by diastereomeric separation.[83a, d]

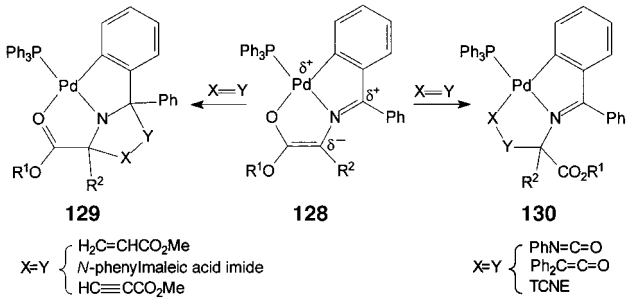
The orthometalated gold complexes $[AuCl_2(dmba)]$ and $[Au(O_2CCH_3)_2(dmba)]$ (dmba = *N*,*N*′-dimethyl benzylamine) exhibit antitumor and antibacterial properties. A model used to investigate the interaction between these complexes and sulfur-containing α-amino acids and peptides is their reaction with L-cysteine and glutathione, which afforded square-planar N,S-chelates.[85] Octahedral, strongly fluorescent Ir^{III} N,O-chelates have been synthesized from the chloro-bridged complex $[Ir(ppy)_2(\mu\text{-}Cl)]_2$ (ppy = 2-phenylpyridine).[82a] Cyclometalation of an amino acid protecting group has been observed with a polynuclear Pd complex.[86] Complexes in which the α-amino acid is itself present as a cyclometalated ligand are comparatively rare; unprotected α-aminocarboxylates form N,O-chelates preferentially. Dinuclear C,N-chelates (**121**) can, however, be isolated from the reaction of *N*,*N*′-dimethyl phenylglycine ethyl ester with Pd^{II} salts[87] and their chemistry was studied.[87a] An analogous Pt^{II} complex with an orthometalated phenylalanine ligand was formed on heating an aqueous solution of *trans*-$K_2[Pt(PheOH)_2Cl_2]$.[88]



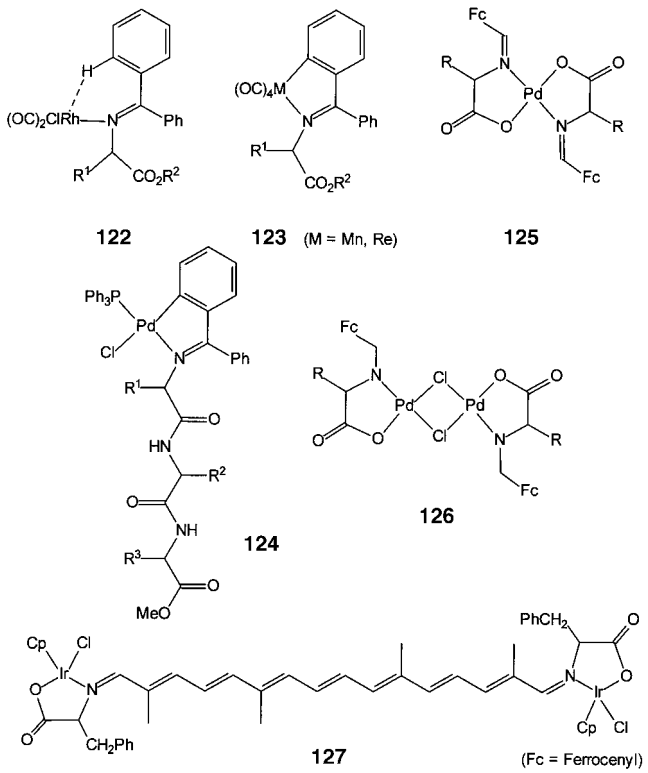
121 (X = Cl, Br, OAc)

The condensation of benzophenone with α-amino acid esters affords Schiff bases (O'Donnell reagents[89]). These compounds possess an activated α-carbon atom and are therefore of interest as precursors for the synthesis of non-biogenic α-amino acids (see Section 3).[89, 90] In organometallic complexes these ligands may be present as monodentate σ-N-donors (**122**),[91] as bidentate C,N-donors (**123**, **124**)[92] or N,O-donors (**125**),[93] and as tridentate C,N,O-donors (**128**).[81, 92b, 95] Reduction of these Schiff bases yields *N*-alkyl α-amino acids. This route can also be used to synthesize *N*-ferrocenylmethyl α-amino acids (see also Scheme 4), which react with $[PdCl_4]^{2-}$ to give the chloro-bridged complexes **126**.[93] The complexation behavior of Schiff base derivatives of unprotected α-amino acids is comparable to that of the free amino acids, with N,O-chelates generally observed.[93] Conjugated diimines have been used to synthesize dinuclear complexes bridged by rigid spacer groups (e.g. **127**).[94]

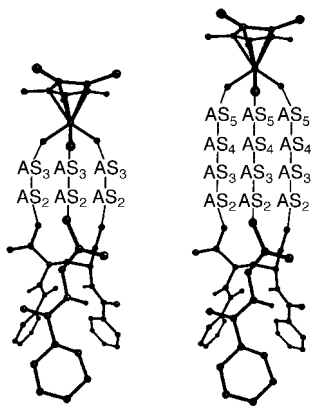
Particularly striking is the reactivity of enolate phosphane complexes of type **128**. As ambident dipoles they react with various dipolarophiles either with coupling of two C – C bonds (**129**) or with the formation of metallaheterocycles (**130**) (Scheme 5).[81, 92b, 95] Analogues of **128**, formed from the diphenylmethylene Schiff bases of dipeptides, can undergo addition to unsaturated hydrocarbons coordinated at cationic metal centers.[96]



Scheme 5. Cycloadditions of Pd complexes with orthometalated α-amino acid Schiff base ligands. TCNE = tetracyanoethylene.



The synthesis of peptides with defined metal binding sites is a first step on the way to synthetic metalloproteins. The necessary preorganization can be achieved through hydrophobic and/or electrostatic interactions as well as through hydrogen bonding, and is often promoted by template effects. Impressive examples are the C_3-symmetric peptide bundles recently reported by Steglich et al.,[97] in which the template is a triglycine derivative linked through a nitrogen atom. The complexation behavior of these ligands was probed initially by their reactions with $[Cp^*TiCl_3]$, which yielded macrobicyclic, likewise C_3-symmetric complexes with ring sizes of up to 32 atoms (**131**, **132**).[98] Ferrocenyl derivatives have also been investigated as a possible way of stabilizing peptide secondary structures. Interest here centers on the β-sheet structures, since the distance between the rings in ferrocene is roughly the same as the N,O-distance between two peptide



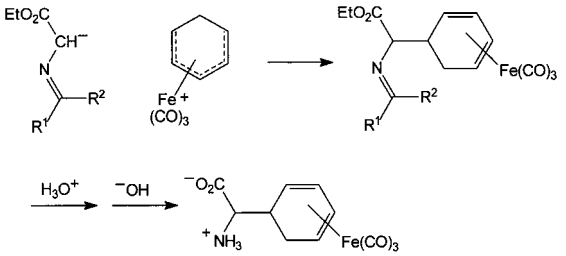
131 **132**

chains. Preliminary results suggest that ferrocenyl bridges, supported by intramolecular hydrogen bonds, are able to lock two α-amino acid esters into a defined conformation.[99, 100]

3. Synthesis of α-Amino Acids

There are few classes of compounds for which so many different synthetic strategies have been developed as α-amino acids and their derivatives. A large proportion of these often stereoselective syntheses are based on traditional organic reactions. Nevertheless, there is also a range of interesting methods based on organometallic transformations. Conceptually, a distinction can be made between two approaches. On the one hand, amino acid side chains can be introduced or modified by reaction with transition metal complexes. Alternatively, the α-amino acid framework can be constructed by organometallic reactions. An overview on this topic is given in a review published in 1995;[101] thus, in the following only the most important methods are summarized in brief, with reference made to some more recent work.

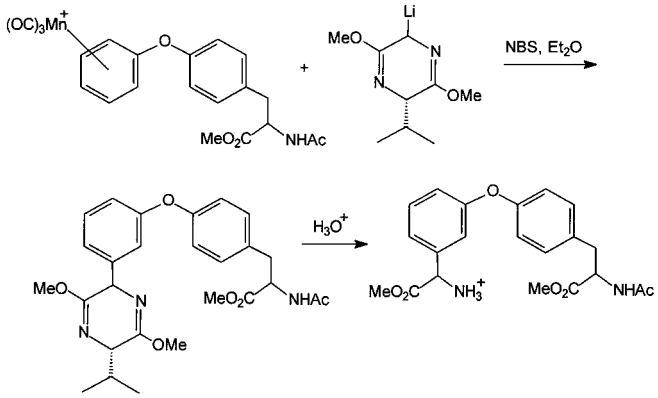
The addition of nucleophilic glycine or alanine synthons to complexes with π-coordinated unsaturated hydrocarbon ligands is a versatile method for the synthesis of α-amino acid derivatives with unusual or metal-containing side chains. The electrophiles that have been used are cationic carbonyl complexes of iron (Scheme 6),[102a–c] manganese,[103] chromium,[102d] and rhenium,[102d] as well as allyl palladium com-



Scheme 6. Synthesis of α-amino acids with cyclohexadienyl side chains by reaction of nucleophilic glycine equivalents with cationic carbonyliron complexes.

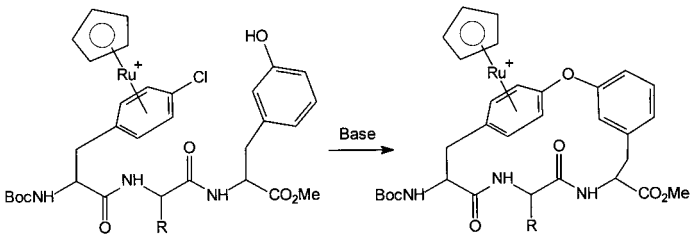
plexes.[102e] This method can be regarded as an"umgepolte" variant of the reaction shown in Scheme 3 (cf. Section 2.4). With the nucleophilic alanine synthetic building block $IZnCH_2CH(NHBoc)CO_2Bn$ (Boc = *tert*-butoxycarbonyl) direct reactions with organic electrophiles are possible. This organozinc reagent can be obtained in a few steps from serine and reacts in the presence of Cu or Pd compounds with a wide range of electrophiles such as alkenyl, alkynyl, and allyl halides, and acid chlorides.[104]

Nucleophilic substitutions with halogenated aryl compounds can be greatly facilitated by η^6 complexation. This method has been used to obtain α-arylglycines by $C_\alpha - C_{aryl}$ coupling of tricarbonylchromium complexes with anionic glycine equivalents.[105b–f] The reaction of $[(C_6H_5FeCp]^+$ with α-amino acid esters affords access to iron-containing *N*-acyl amino acids.[105a] Of particular interest in this context is the activation of chloroaryl compounds by the $Mn(CO)_3$ fragment. These complexes undergo nucleophilic substitution with aryl alkoxides.[106] The diaryl complexes thus obtained can be transformed into the corresponding α-arylglycine derivatives by reaction with Schöllkopf's chiral glycine enolates (Scheme 7).[106a, b] Diaryl ether-bridged amino acids of this type are of high synthetic value as building blocks for glycoprotein antibiotics such as vancomycin.



Scheme 7. Synthesis of aryl ether bridged phenylglycine derivatives by activation with $[Mn(CO)_3]^+$ fragments. NBS = *N*-bromosuccinimide.

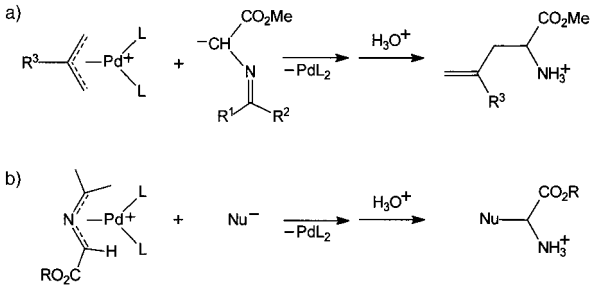
Aryl ether bonds can also be constructed through activation with CpFe and CpRu fragments;[107] the reagent of choice has proven to be the Ru complex (Scheme 8). The introduction



Scheme 8. Synthesis of cyclic aryl ethers from halogenated [CpRu] sandwich complexes.

of this group and the coupling reaction proceed under very mild conditions. Furthermore, multiple substitutions are possible. S_NAr reactions such as these have been exploited in the formal total syntheses of the protease inhibitors K13 and OF4949III[108] and in the synthesis of model systems for the antibiotics teicoplanin,[109] ristocetin,[110] and vancomycin.[111]

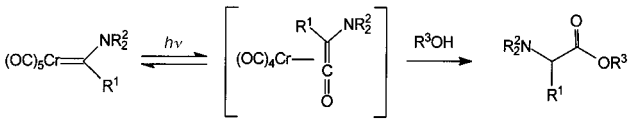
A catalytic version of the type of reaction shown in Scheme 6 is the Pd^0-catalyzed alkylation of Schiff bases of formula $R^1_2C{=}NCH_2CO_2R^2$ with allyl esters, allyl halides, or allyl carbonates.[112] The C–C coupling occurs through nucleophilic attack of the deprotonated Schiff base on a η^3-allyl Pd complex. The imino ester formed is converted into the corresponding α-amino acid ester on acid hydrolysis (Scheme 9a). Enantioselective alkylations can be achieved with optically active Schiff bases and/or phosphanes.[113] A variant of this reaction permits the synthesis of α-amino acid esters with 1,3-dienyl or styryl-substituted side chains; allenes are initially coupled with aryl or vinyl halides and then allowed to



Scheme 9. Synthesis of α-amino acids by a) reaction of cationic allyl-Pd complexes with nucleophilic glycine equivalents or by b) reaction of azaallyl-Pd complexes with C-nucleophiles.

react with nucleophilic glycine equivalents.[114] η^3-Allyl Pd complexes can also function as α-amino acid building blocks. In the reaction of acetylated Schiff bases with Pd^0 phosphane complexes the azaallyl Pd complexes formed initially react with C-nucleophiles to give the corresponding α-amino acid derivatives (Scheme 9b).[115]

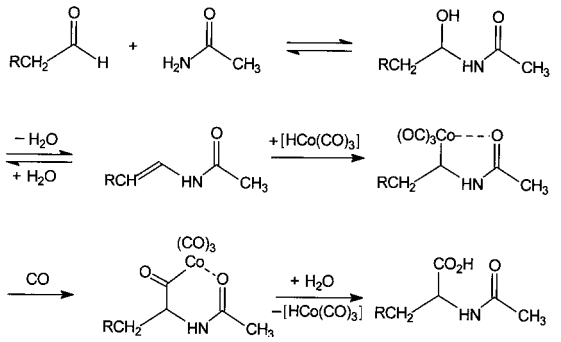
A particularly versatile method for the synthesis of α-amino acids (and peptides: see Section 4) has been developed by Hegedus et al.,[116] in which the photochemical activation of aminocarbene Cr complexes leads to CO insertion products with ketene-like reactivity; reaction with alkoxides affords α-amino acid esters (Scheme 10). By using chiral auxiliaries,



Scheme 10. Synthesis of α-amino acid esters by photochemically induced reaction of aminocarbene complexes with alcohols.

stereoselective reactions with high optical yields are possible; optically active oxazolidines are particularly suitable. Aminocarbene Cr complexes can also be used to synthesize *C*-alkylidenamino ketimines, which yield α-amino acid amides on hydrolysis.[117]

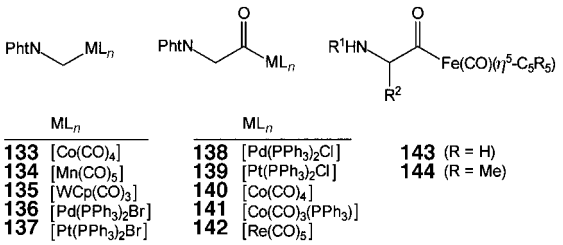
In 1971 Wakamatsu et al. reported the cobalt carbonyl catalyzed amidocarbonylation of aldehydes under the conditions of the oxo synthesis (H_2, CO, $[HCo(CO)_4]$ as catalyst).[118] This reaction, subsequently named Wakamatsu reaction, leads to *N*-acyl α-amino acids (Scheme 11),[119] and can be used in combination with other



Scheme 11. Postulated mechanism for the cobalt-catalyzed amidocarbonylation of aldehydes.

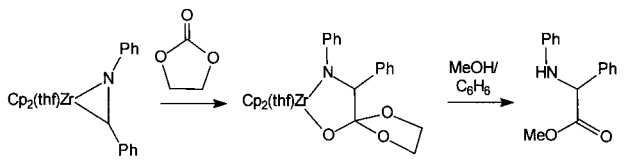
catalytic reactions. Instead of the aldehyde, oxiranes and allyl and homoallyl alcohols can also be used.[120] These substrates rearrange to the corresponding aldehyde with involvement of a cocatalyst. Because the amidocarbonylation conditions correspond to those used in hydroformylation, olefins[121] or benzyl chloride[122] can also be used. In a more recent variant of the amidocarbonylation, Pd catalysts are used in combination with ionic halides.[123] This procedure can be carried out under relatively mild conditions, does not require hydrogen, and is characterized by its high efficiency. Another Pd-catalyzed reaction, the homogeneously catalyzed hydrocarbalkoxylation of *N*-alkenyl amides, affords access to *N*-protected α-amino acid esters.[124]

The intermediates in the amidocarbonylation are thought to be aminomethyl and aminoacetyl complexes (Scheme 11). Compounds of this type have been isolated and characterized. Thus, *N*-phthaloylmethyl chloride and *N*-phthaloylglycyl chloride yielded the complexes **133**–**135** and **140**–**141** on reaction with carbonyl metalates,[125] and complexes **136**–**139** by oxidative addition to Pd^0 and Pt^0 compounds.[126] In



agreement with the postulated mechanism the acetyl compound **140** yields phthaloylglycine with water and dipeptides with α-amino acid esters.[125b] The reaction of mixed anhydrides of N-protected α-amino acids or dipeptides with $[CpFe(CO)_2]^-$ (Fp^-) or $[Cp^*Fe(CO)_2]^-$ (Fp^{*-}) affords the iron acetyl complexes **143** and **144**.[127] After removal of the N-protecting group the relatively stable compounds **144** can be reacted with activated amino acids to give dipeptides.[127b] Oxidative cleavage of **143** and **144** yields aldehydes, with loss of the amino and acyl groups.[127a]

The construction of the α-amino acid backbone by connecting a bond between the α-C atom and the carboxylate C atom can also be achieved through reaction of the CO_2 building block ethylene carbonate with zirconocene imine complexes (Scheme 12).[128] Such an insertion is also possible

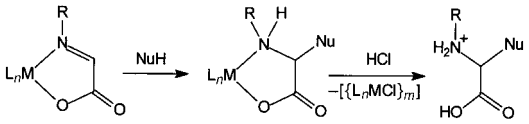


Scheme 12. Construction of α-amino acids at the metal center by reaction of zirconocene imine complexes with the CO_2 building block ethylene carbonate.

with CO_2 directly, though cleavage of the ligand from the metal fragment has proven difficult here. With the use of optically active bridged bicyclopentadienyl ligands this insertion proceeds stereoselectively with over 96% *ee*. A similar

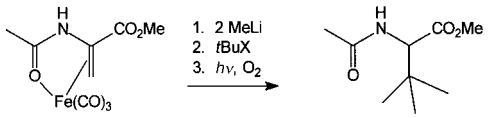
reaction, the coupling of ketimines with CO_2, can be achieved in the presence of ytterbium metal, yielding α-aminocarboxylate Yb complexes. [129] The free amino acid is then obtained by HCl cleavage.

The addition of nucleophiles to the imino-C atom of α-imino carboxylic acid derivatives is an often used method for the synthesis of α-amino acids. In this reaction, nucleophilic attack is promoted by electron-withdrawing groups. Alternatively, the imino group can be activated by coordination to transition metals. These compounds are generally prepared by the template-directed, metal-mediated condensation of amines with 2-oxocarboxylates or by elimination reactions. Reactions with nucleophiles lead to α-aminocarboxylate complexes; the ligand can then be cleaved off by addition of acid (Scheme 13). Optically active complexes merit particular attention as they allow these C – C couplings to be carried out stereoselectively. In a kind of umpolung reaction, α-imino esters undergo reaction with alkyl halides after coordination to $Fe(CO)_4$.[131]



Scheme 13. Synthesis of α-amino acids by reaction of α-iminocarboxylate complexes with nucleophiles.

Iron carbonyl complexes have also been used to synthesize β,β,β-trialkyl-α-amino acids: reaction of acetamidoacrylate – $Fe(CO)_3$ complexes with two equivalents of methyllithium, a tertiary alkyl chloride, and subsequent oxidative workup affords the corresponding amino acid derivatives in good yield (Scheme 14).[132]



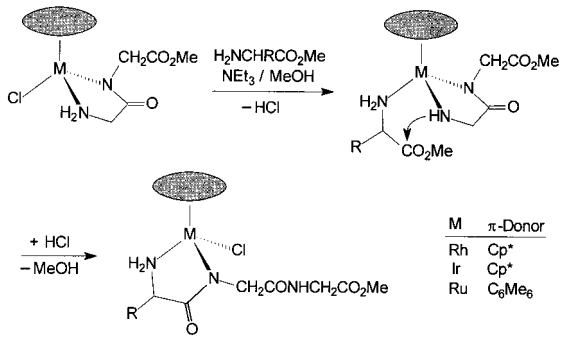
Scheme 14. Synthesis of α-amino acids with sterically demanding side chains using acetamidoacrylate – $Fe(CO)_3$ complexes.

Finally, reference should be made here in brief to some other reactions in which organometallic complexes are present solely as reactive intermediates. One of the best studied methods for the asymmetric synthesis of α-amino acids is the hydrogenation of prochiral dehydroamino acid derivatives. The use of optically active diphosphane – Rh and -Ru complexes allows these reactions to be carried out stereoselectively in excellent optical yield (up to 100% *ee*).[133] Intermediates in this reaction are α-metalated amino acid derivatives (see also **15**, **105**, **106**).[133] Transition metal catalyzed reactions have also been used to functionalize amino acid side chains. With the use of α-amino acids with stannylated or halogenated side chains, Pd^0-catalyzed cross-coupling and, thus, selective lengthening of the side chain is possible.[134] Metathesis reactions with ruthenium carbene complexes have been used to convert *N*-allyl-, *C*-allyl-, and *C*-vinylalkyl-substituted amino acids or peptides into cyclic, conformationally rigid compounds.[135] Simple homoallyl glycine derivatives can also be modified through cross-metathesis reactions.[136] Conformationally stable phenylalanine derivatives have been obtained by Pd^0-catalyzed intramolecular C – C couplings.[137] Chiral ferrocenylphosphane ligands allow β-hydroxy α-amino acids to be synthesized stereoselectively through Au^I- or Ag^I-catalyzed aldol reactions of α-isocyanomethyl esters with aldehydes.[138] If a planar-chiral tricarbonylchromium benzaldehyde complex is used as the aldehyde, the reaction yields—even without the addition of a further chiral auxiliary—organometallic oxazolines with high diastereoselectivity, which can likewise be transformed into β-hydroxy-α-amino acids.[139]

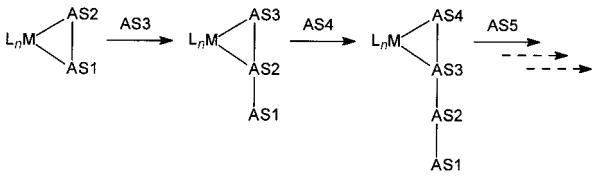
4. Synthesis of Peptides

The selective synthesis of peptides in the coordination sphere of transition metals was first reported in 1967.[140] This type of reaction, which has since been extensively studied, has attained only secondary importance as a synthetic method, though it has been proposed as a possible mechanism for the formation of peptides under prebiotic conditions.[140e] Organometallic complexes have so far been used relatively rarely for the synthesis or modification of peptides. Nevertheless, there are a number of noteworthy reactions, which are described below.

Half-sandwich complexes of the elements Rh, Ir, and Ru have been used to develop a sequence-specific peptide synthesis,[47] in which N,N′-coordinated peptides undergo selective chain lengthening at the N-terminus by reaction with α-amino acid esters. The linking of the peptide bond requires neither activating reagents nor protecting groups; the peptide ester formed can then be cleaved from the metal complex without racemization. Scheme 15 shows the postulated reaction mechanism. This template-directed condensation proceeds through nucleophilic attack of an amino anion on the carbonyl group of the η^1-N-coordinated amino acid ester. In principle, the mechanism shown in Scheme 15 permits further chain-lengthening as desired; with repeated addition of α-amino acid esters the coordinated peptide is successively lengthened at the N-terminus, the half-sandwich complex functioning solely as a catalyst (Scheme 16). Such a



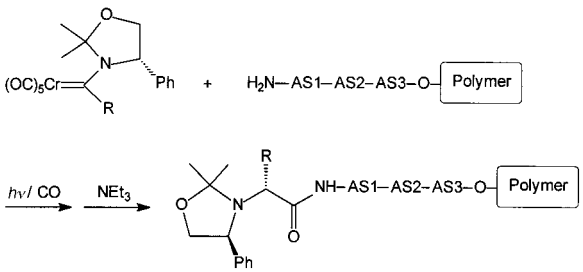
Scheme 15. Sequence-specific peptide synthesis at chiral half-sandwich complexes of the elements Rh, Ir, and Ru.



Scheme 16. Metal-catalyzed construction of peptides by successive reaction of α-amino acid esters with coordinated peptide complexes.

reaction sequence has already been used to synthesize peptides with chain lengths of up to nine amino acid residues at the [(*p*-cymene)RuCl] fragment.[47d] Recently the Ni^0-catalyzed polymerization of α-amino acid-*N*-carboxyanhydrides (Leuchs anhydrides) was reported; it leads to block copolypeptides with well-defined sequences.[141a, b] The palladium copolymerization of imines with CO was suggested as a way to polypeptides.[141c]

In Section 3 a method was described that allows α-amino acid esters to be synthesized by the photochemically induced alcoholysis of aminocarbene chromium complexes (see Scheme 10). If, instead of the alcohol, the reaction partner is an α-amino acid ester or a peptide with an unprotected N-terminus, di- or oligopeptides are formed in good yield (Scheme 17).[116] This process enables non-biogenic or labeled

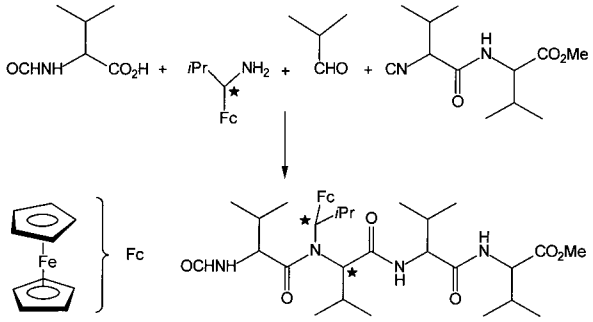


Scheme 17. Diastereoselective incorporation of synthetic α-amino acids in solid-phase peptide syntheses by reaction with chiral aminocarbene complexes.

α-amino acids to be incorporated into peptides selectively. Compared with alternative methods, a number of advantages are apparent; with the appropriate choice of chiral auxiliary the configuration of the incoming amino acid can be determined. Furthermore, the coupling proceeds in good yield even with sterically hindered amino acids and is compatible with the conditions of solid-phase[142] or polyethyleneglycol-supported[143] peptide syntheses.

Carboxylate complexes of the early d^0-transition metals are similar to activated esters in their reactivity, which means they can be used as acylation reagents. The use of organometallic $\{Cp_2Ti\}$-*N*-acyl aminocarboxylate complexes in peptide syntheses was first reported in 1990.[54a] Reaction with methyl L-alaninate under relatively drastic conditions (THF, reflux) affords dipeptide esters in moderate yield. Considerably higher reactivity is shown by carboxylate complexes of type $[Cp^*TaCl_3(O_2CCHR^1NHR^2)]$,[144] which react with α-amino acid esters even at low temperatures. The yield and degree of racemization in this condensation reaction are comparable with that of standard systems such as DCC/HOBt (HOBt = hydroxybenzotriazole).

In the work described so far the organometallic complex fragment was directly involved in the formation of the new peptide bond. Another option, however, is to use it as chiral auxiliary. In a series of publications Ugi et al. have described the synthesis of peptides by means of stereoselective four-component reactions,[145] in which an N-protected α-amino acid, a chiral amine, an aldehyde, and an α-isocyanoacyl α-amino acid derivative undergo condensation in a one-pot reaction to give an N-substituted tetrapeptide (Scheme 18). With the use of α-ferrocenylalkyl amines as the chiral auxiliary, these Ugi reactions can be carried out almost completely diastereoselectively.

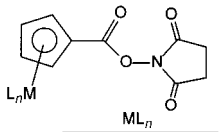


Scheme 18. Ferrocenyl derivatives as chiral auxiliaries in Ugi four-component reactions.

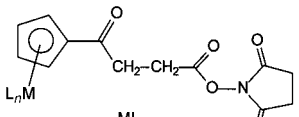
5. Use as Labeling Reagents

The ligands (CO, NO, unsaturated hydrocarbons) and the metal atom offer means by which organometallic complexes can be detected selectively even in small quantities. This has led to the growing use of these compounds as markers in biochemical or biological investigations. Areas of application include immunological assays, X-ray crystallography or electron microscope studies, and the characterization of active centers. Such compounds can also be used as radiopharmaceuticals, provided they are sufficiently stable under physiological conditions and are able to undergo covalent coupling with the appropriate biomolecule in the presence of a suitable coupling reagent. The following section presents the various classes of compound described together with their areas of application.

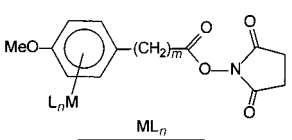
One of the simplest ways of functionalizing peptides and proteins is by acylation of free amine groups (e.g. lysine side chains). Efficient reagents for this acylation have proven to be succinimidyl esters. Through coupling of this reactive group with transition metal complexes, a range of organometallic markers have been synthesized, such as the cyclopentadienyl complexes **145**–**151**,[146] the sandwich complexes **152** and **153**,[147] the alkyne clusters **154**–**156**,[148] and the bimetallic Re complex **157**.[149] These compounds are prepared from the corresponding acids by reaction with *N*-hydroxysuccinimide in the presence of DCC. A measure of their reactivity can be obtained from their reaction with α-amino acid esters. Organometallic complex fragments can also be incorporated into peptides by coordination to the π-structures of amino



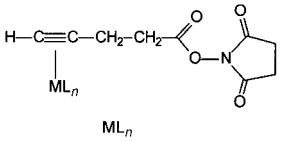
	ML_n
145	$[Re(CO)_3]$
146	$[Mn(CO)_3]$
147	$[Mo(CO)_3Me]$
148	$[W(CO)_3Me]$
149	$[Fe(CO)_2Me]$



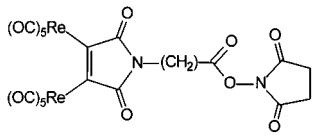
	ML_n
150	$[Re(CO)_3]$
151	$[Mn(CO)_3]$



	ML_n
152	$[Cp^*Ir^{2+}]$
153	$[Cp^*Ru^+]$



	ML_n
154	$[Os_3(CO)_{10}]$
155	$[Co_2(CO)_6]$
156	$[Mo_2Cp_2(CO)_4]$



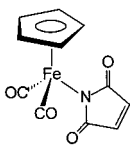
157

acid side chains, as demonstrated by Sheldrick et al. (see Section 2.4).[58]

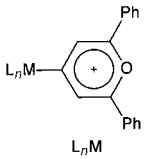
The IR spectra of the carbonyl complexes **145**–**151** and **157** show extremely intense, characteristic absorption bands in the region between 1900 and 2100 cm^{-1}. Biological molecules, by contrast, have a so-called spectroscopic window in this region, which means that substrates labeled with these complexes can be detected by Fourier transform infrared spectroscopy (FTIR). The detection limit for this is in the picomole region with modern FT spectrometers. This was used by the group of Jaouen as the basis for the development of a carbonylmetalloimmunoassay (CMIA).[1c, 150] By means of competitive antigen-antibody reactions with an organometallic hapten, hormones or other pharmacologically relevant substances can be quantitatively detected. CMIA has a number of advantages over classical immunoassays: firstly, no radioactive compounds are necessary,[151] and secondly, with the use of different markers, several immunoassays can be performed in parallel.[152] This is possible because different carbonyl complexes can be determined simultaneously by their characteristic absorption bands.

Transition metal complexes of type **145**–**156**, the metal-rich, and hence electron-rich clusters **154**–**156** in particular, are of interest not only for their potential CMIA applications, but also as labels for X-ray or electron microscope studies.[153] As a model system a globular protein (67 kDa) was labeled with **154**;[148a] here an average of 20 clusters per protein were incorporated.

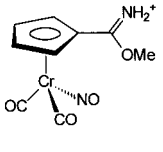
In addition to the above-mentioned complexes with active ester groups, other electrophilic complexes with potential applications as biomarkers have also been described. The $[CpFe(CO)_2]$ complex **158** reacts with α-amino acids with nucleophilic addition of NH- or SH-functions to the double bond.[154] Coordination of the $[CpFe(CO)_2]$ fragment (Fp) to tryptophan methyl ester can also be accomplished by direct reaction with FpI under basic conditions.[155] Labeling with carbonyl or ferrocenyl complexes can be achieved by the



158

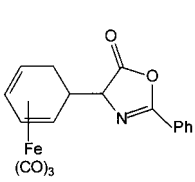


	L_nM
159	$[CpMn(CO)_3]$
160	$[CpRe(CO)_3]$
161	$[Cp_2Fe]$

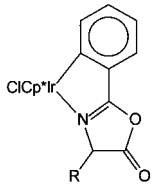


162

reaction of free amino groups with the pyrilium salts **159**–**161**,[156] which yields pyridinium salts. The succinimidyl ester and pyrilium complexes have two drawbacks: they are relatively poorly soluble in water and secondly, this functionalization of the free amino group changes the overall charge on the corresponding protein. Therefore the water-soluble metal carbonyl imido ester **162** was synthesized.[157] This complex reacts with amino groups to form amidines, which are positively charged under physiological conditions. A disadvantage here, however, has proven to be the low stability of the $[CpCr(NO)(CO)_2]$ fragment. α-Amino acids can also be labeled with tricarbonylchromium complexes by η^6-complexation of $Cr(CO)_3$ to *N*-benzoyl protecting groups.[35a] The oxazolinone complexes **163** and **164** can likewise be regarded as activated esters;[70a, 158] they react with α-amino acid esters under basic conditions to form transition metal-containing dipeptides.[159]



163



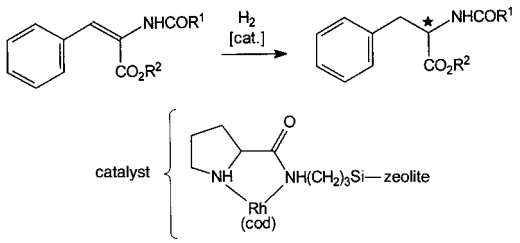
164

Cationic iron carbonyl complexes of general formula $[(\eta^5\text{-}RC_6H_6)Fe(CO)_3]^+$ react with nucleophiles to form neutral diene complexes. In Section 2.4 it was described how this reaction can be used to synthesize α-amino acids with unusual side chains (see Scheme 6). Cationic iron complexes of this type can, however, also be used as a way of selectively labeling peptides and proteins;[160] a clear preference for cysteine and histidine has been established. In addition to traditional analysis techniques, electrospray mass spectrometry has now emerged as a suitable method for characterizing these adducts.[161] The functionalization of peptides and proteins with ferrocenyl groups is of interest on account of the electrochemical properties of these complexes,[162] and can be accomplished by using various derivatives with activated ester groups.

6. Use as Catalysts

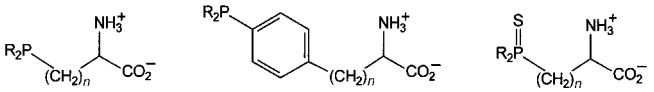
The incorporation of α-amino acids or their derivatives into catalytically active transition metal complexes affords a simple and economical way of accessing chiral compounds with potential applications in enantioselective catalysis.[163] One such example is the heterogeneous hydrogenation of prochiral olefins with Rh^I proline amide complexes linked to a

modified zeolite through a spacer.[164] These compounds have proven to be efficient and highly enantioselective catalysts (Scheme 19). Comparable immobilized catalysts have also been used in the hydrogenation of arenes,[165] in the addition of diethylzinc to enones,[166] and in cyclopropanations.[167]



Scheme 19. Enantioselective hydrogenation of acetamidocinnamate esters using immobilized proline-amide-Rh^{I} complexes.

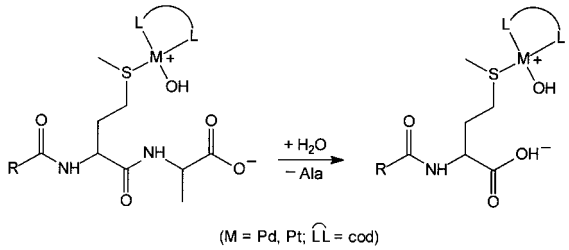
Many homogeneous catalysis processes use electron-rich complexes of the late transition metals, and phosphane ligands have proven particularly useful. For this reason, α-amino acids, particularly the relatively rigid proline, have often been functionalized with phosphane groups.[163e] An interesting more recent approach is the coupling of alkyl- or arylphosphanes with α-amino acid side chains (**165**, **166**),[168] which allows the synthesis of peptides with defined binding sites for catalytically active transition metals.[169] In solid-phase peptide syntheses compounds of the type **167** have proven useful,[169] since they can subsequently be reduced to the corresponding phosphanes.



165 **166** **167**

The application of the methods and concepts of combinatorial chemistry in the search for new metal-containing catalyst systems may yet lead to the kind of breakthrough in this area seen in recent years in bioorganic and pharmacological chemistry.[170] Nevertheless, up to now there have been only isolated successes. A first important step in this direction is the assembly of catalyst libraries. An obvious line of approach is the use of ligands with modular structures. α-Amino acids are particularly attractive candidates as building blocks for such ligands; not only are they optically active and commercially available in both enantiomeric forms, they can be used as the basis, using only few fragments, for assembling libraries of great diversity. It is therefore not surprising that many recently published studies on combinatorial catalysis make use of this synthetic concept.[171]

In organometallic catalysis α-amino acids and peptides are not only used as ligands, but are also the subject of numerous studies in which they are the substrate. Particularly interesting are metal complexes capable of cleaving peptides hydrolytically, and where possible, regioselectively. Such reagents could find use as chemical alternatives to proteolytic enzymes in analytical biochemistry. Pt^{II} and Pd^{II} aqua complexes in particular have proven useful as synthetic metallopeptidases.[172] These compounds coordinate to the heteroatom of side chains and catalyze the regioselective hydrolysis of the neighboring amide bond. Such cleavage can also be accomplished with organometallic complexes of type $[M(cod)(D_2O)_2]^{2+}$ (M = Pd, Pt) (Scheme 20).[173]



Scheme 20. Regioselective hydrolysis of peptides.

Because of the long half-life of the hydrolysis of amide bonds under neutral conditions, many studies employ activated esters initially. Thus, *N*-Boc-methionine *p*-nitrophenyl ester has been shown to hydrolyze up to 535 times more rapidly in the presence of orthometalated Pd and Pt complexes than in control experiments without addition of metal complexes.[174] In these reactions no turnover is observed, as the complexes are coordinated irreversibly to the sulfur-containing methionine side chain. Chloro-bridged half-sandwich complexes of the elements Rh and Ir have proven useful as catalysts for ester exchange reactions with α-amino acid esters.[48b] Transesterification can then be achieved through nucleophilic attack by the alcohol on the likewise coordinated carbonyl group or through a template reaction with the coordinated alcohol.

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