Review

Metal Complexes of Biologically Important Ligands, CLXXII [1]. Metal Ions and Metal Complexes as Protective Groups of Amino Acids and Peptides – Reactions at Coordinated Amino Acids

Wolfgang Beck

Department Chemie und Biochemie der Ludwig-Maximilians-Universität München, Butenandtstraße 5 – 13, 81377 München, Germany

Reprint requests to Prof. Dr. W. Beck. E-mail: wbe@cup.uni-muenchen.de

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Dedicated to Professor Hubert Schmidbaur on the occasion of his 75th birthday

The introduction of protective groups into multifunctional molecules, *e. g.* into amino acids for peptide synthesis, and their removal are one of the most important techniques and strategies in Organic Chemistry [2]. Amino acids, their anions and derivatives are versatile ligands, and the leading idea to protect the N- or C-terminus of amino acids by metal ions or by metal complexes has opened interesting chapters which reach from classical coordination and bioinorganic chemistry to modern organometallic and bioorganometallic chemistry [3].

Key words: Amino Acids, Peptides, Protective Groups, Metal Ions, Metal Complexes

Contents

1. Metal Ions as Protective Groups

1.1. Copper(II) chelate complexes of diamino carboxylic acids (ornithine, lysine)

A very valuable [4] and convencient method for the selective protection of the α-amino group in α,ω-diamino acids was introduced by Kurtz in 1937 [5 – 7] by formation of copper(II) chelate complexes of lysinate and ornithinate. In these stable chelate complexes only the α-amino group is coordinated while the ω-NH_2 group is free to react with *e. g.* acyl halides. Already in 1909, Fischer [8a], Tschugaeff [8b] and Ley [8c] recognized that – for steric reasons – only α- and β-amino acids form copper chelate complexes whereas γ-, δ- and ε-amino acids

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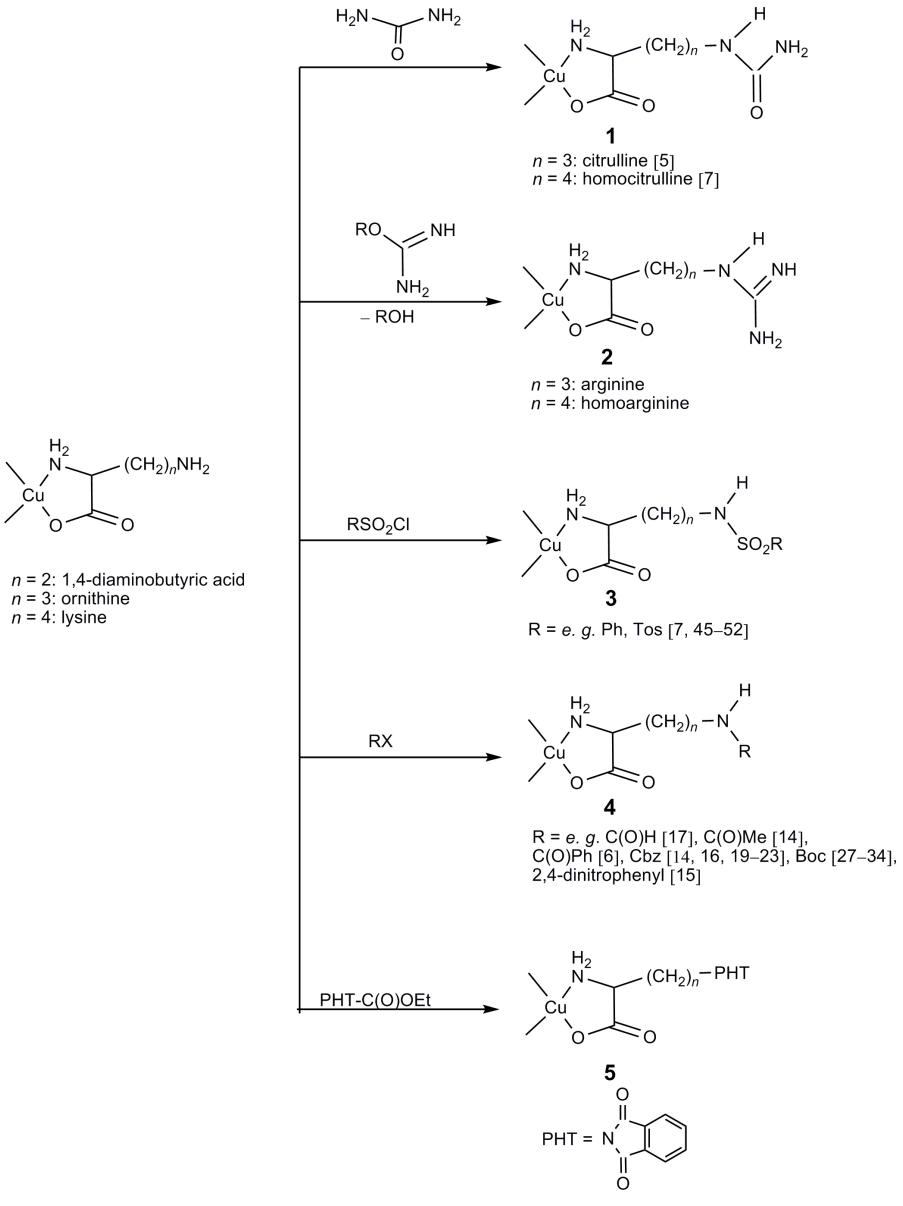


Scheme 1. Usually *trans-bis*(chelate) complexes are formed. Only one half of the ligands is shown in some of the formulas in the schemes.

do not. The copper(II) chelates have been characterized several times [9], and the structures of *trans*-$\{Cu[NH_2CH(CO_2)(CH_2)_nNH_3]_2\}^{2+}$ ($n = 3, 4$) with zwitterionic ligands have been determined by X-ray diffraction [10].

Kurtz reported in his first papers the synthesis of citrulline (**1**) by condensation of the δ-amino group of copper(II) ornithinate with urea, the removal of copper as copper sulfide by hydrogen sulfide [5] and the reaction of benzoyl chloride with copper lysinate (**4**) and isolation of N^{ε}-benzoyl lysine [6] (Scheme 1).

Later, Kurtz [7] demonstrated the usefulness of his copper method by the synthesis of homocitrulline (**1**) and of α-amino-carbamido butyric acid from copper lysinate or copper 1,4-diaminobutyric acidate with urea, by the reactions of the chelate copper complexes of lysine, ornithine and 1,4-diamino butyric acid with phenyl isocyanate, benzoyl chloride (**4**), *p*-nitrobenzoyl chloride and phenylsulfonyl chloride (**3**), and by the formation of arginine, and homoarginine (**2**) with *O*-alkyl isouronium halides ($[H_2NC(=NH_2)OR]^+ Cl^-$). The synthesis of arginine from copper ornithi-

nate and *O*-methyl isouronium chloride was independently reported [11, 12]. Later, ω-carbamido derivatives of the diamino amino acids were also obtained from the copper chelates and potassium cyanate [13].

Neuberger and Sanger (as a student) [14] prepared N^{ε}-acetyl lysine and N^{ε}-carbobenzoxy lysine (**4**) from copper lysinate, and Sanger used "his" dinitrofluorobenzene (DNFB) reagent [15] for the identification of the free amino group of ornithine in the cyclic peptide gramicidine S by the preparation of N^{δ}-2,4-dinitrophenyl ornithine from copper ornithinate and DNFB.

The copper method for the derativization of diamino carboxylic acids has been widely used (**1** – **5**) to achieve the selective introduction of organic protective groups into the ω-NH_2 position for the synthesis of α-peptides which contain ornithine or lysine. A first example was reported by Synge [16], *e. g.* the synthesis of L-valyl-L-ornithine by reaction of carbobenzoxy-L-valyl chloride with N^{δ}-carbobenzoxy-L-ornithine methyl ester. For the selective reaction at the side chain under protection of the α-amino group of lysine, ornithine and (rather rarely) 1,4-diamino butyric acid in their copper complexes the following reagent were used: Ethylformate [17], acetic acid anhydride [14], phenylacetyl chloride [18], benzoyl chloride [6, 9c], carbobenzoxy chloride (benzyloxycarbonyl chloride, benzyl formic acid chloride) [14, 16, 19 – 23], *p*-nitrobenzyl chloroformate [24], *p*-nitrophenyl-*o*-bromobenzyl carbonate [25], *o*-chlorobenzyl chloroformate [26], di-*tert*-butyl dicarbonate($(Boc)_2O$) [27 – 34] (which was introduced by Moroder and Wünsch [27]), *tert*-butylazidoformate (*tert*-butyloxycarbonylazide BocN_3) [35], *tert*-butyloxycarbonyl fluoride (BocF) [36], allyl chloroformate [37, 38], *p*-(*p*′-methoxyphenyl-azo)-benzyloxycarbonyl chloride (to give colored derivatives) [39], β,β,β-trichloro-ethyloxycarbonyl chloride [40], fluorenylmethoxycarbonyl azide (Fmoc-N_3) [41], biotin acid chloride [42], isonicotinyl-*p*-nitrophenyl carbonate [43], 2-(trimethylsilyl)ethyl-4-nitrophenyl carbonate [44].

The reaction at the ω-NH_2 group of diamino acids in their copper complexes with benzene sulfonyl chloride and toluene sulfonyl chloride (**3**) was applied several times in amino acid and peptide chemistry [7, 45 – 52], *e. g.* for the synthesis of N^{α}-trifluoracetyl-N^{ε}-tosyl-L-lysine [53]. Also 2-thiophenecarbonyl chloride [54, 55], *p*-bromobenzene sulfinylchloride [56], 8-quinoline sulfonyl chloride [54, 55], 4-methoxy-2,3,6-trimethylbenzene sulfonyl chloride [56], and *p*-$MeC_6H_4CH_2SO_2Cl$ [56] were used.

Attention should be given to the N^{ω}-phthaloyl-protected diamino acids which have been obtained by reactions of the *N*,*O*-copper-chelates with carboethoxycarbonylphthalimide [57] or with phthalimide to give **5** and N^{ω}-phthaloyl-$N(CH_2)_nC(H)(NH_2)COOH$ after easy removal of Cu(II) with hydrochloric acid [22, 58 – 60].

Further examples of N^{ω}-protected diamino acids and their application in peptide synthesis have been compiled by Wünsch in his excellent volume of Houben-Weyl [4].

Also reactions of the ε-amino group of the complex Cu(β-lysinate)$_2$ (a 6-membered chelate ring) with carbobenzoxy chloride have been reported [61].

The reactions of copper(II), nickel(II), and zinc(II) *N*,*O*-lysinate and tyrosinate complexes with aryl diacid dichlorides afforded polymeric complexes **6** [62, 63]. The liberated ω,ω'-terephthaloyl diamido diamino acids **7** (Scheme 2) have been reacted as *bis*(*N*,*O*-chelate) ligands with chloro-bridged half-sandwich complexes to give ligand-bridged, dinuclear compounds [63].

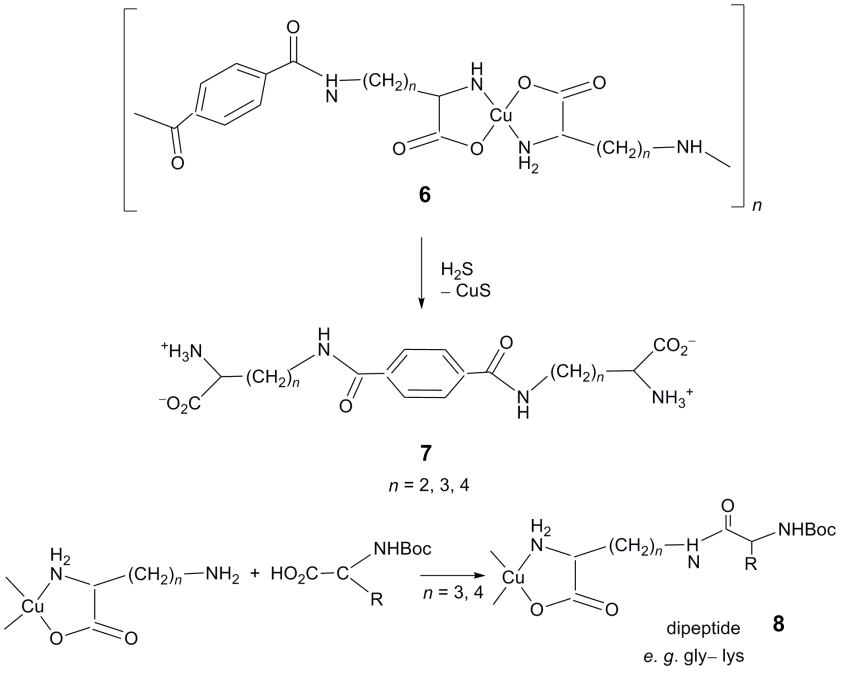
Another important application of the copper(II) chelate of diamino carboxylates is the formation of dipeptides **8** (Scheme 2) by condensation (using the mixed anhydride method with ClC(O)OEt) of the free ω-NH_2 group with the carboxylic group of amino acids to give finally (after removal of copper) *e. g.* N^{ε}-(glycyl)-lysine [64], N^{ε}-(γ-glutamyl)-lysine [65], N^{δ}-(γ-glutamyl)-ornithine [66], N^{δ}-(α-glutamyl)-ornithine [66], N^{δ}-(β-aspartyl)-ornithine [67], N^{ε}-(α-glutamyl)-lysine [68], N^{ε}-(β-aspartyl)-lysine [68].

Similarly, the ε-NH_2 group of the copper complex of β-lysinate has been coupled with the carboxylic group of (NH_2-protected) β-lysine to give N^{ε}-(β-lysyl)-β-lysine [69].

Copper(II) complexes were also used for the preparation of N^{ε}-(Boc or Cbz) protected derivatives of 5-hydroxylysine, using $(Boc)_2O$ or CbzCl [70 – 76]. The copper complex of lysinate was attached to DNA [77] and to a chlorosulfonated polymer [78] *via* the ε-amino group.

An improved synthesis of "lysinoalanine" $H_2NC(H)(CO_2H)(CH_2)_4NHCH_2C(H)(CO_2H)NH_2$ by addition of 2-acetamido acrylate to a mixed (lysinate)(alaninate)copper(II) complex was reported [79].

Lysine was coupled to dextran using copper lysinate [80]. The copper complexes of lysine and or-



Scheme 2.

nithine were reacted with a polysaccharide, activated by cyanogen bromide [81]. The reaction of copper lysinate with itaconic anhydride gave – after removal of Cu^{2+} – a monomer, suitable for the synthesis of lysine-containing polymers [82].

1.2. Copper(II) chelates of aspartic and glutamic acid

Kurtz [7] already suggested the use of copper complexes of amino dicarboxylic acids for the protection of the α-carboxylic group, and this method was applied for the synthesis of γ-benzyl glutamate [83] and for a series of substituted γ-benzyl-glutamates and β-benzyl-aspartates **9** [84, 85]. An improved method for many other esters obviates the need for isolation of the copper complexes [86] (Scheme 3). Another method for the synthesis of ω-esters of glutamic and aspartic acids includes the copper(II)-catalyzed hydrolysis of α,ω-diesters whereby the copper(II) chelate of the mono ester is formed [87] (Scheme 3). Early, the structures of the dianionic copper complexes of aspartate and glutamate $\{Cu[O_2CCH(NH_2)(CH_2)_n CO_2]_2\}^{2-}$ were correctly formulated [84, 86, 88]. In the crystals of the polymeric Cu(L-asp)$(H_2O)_2$ [89] and Cu(L-glu)(H_2O) [89] the copper(II) ion forms a five- membered chelate ring with the α-NH_2 and α-carboxylate groups and is linked to an oxygen atom of the side chain carboxylate group of a neighboring amino-dicarboxylate dianion. Also reactions at the uncoordinated carboxylic group of Co(glutamate)$_3$ have been studied [90].

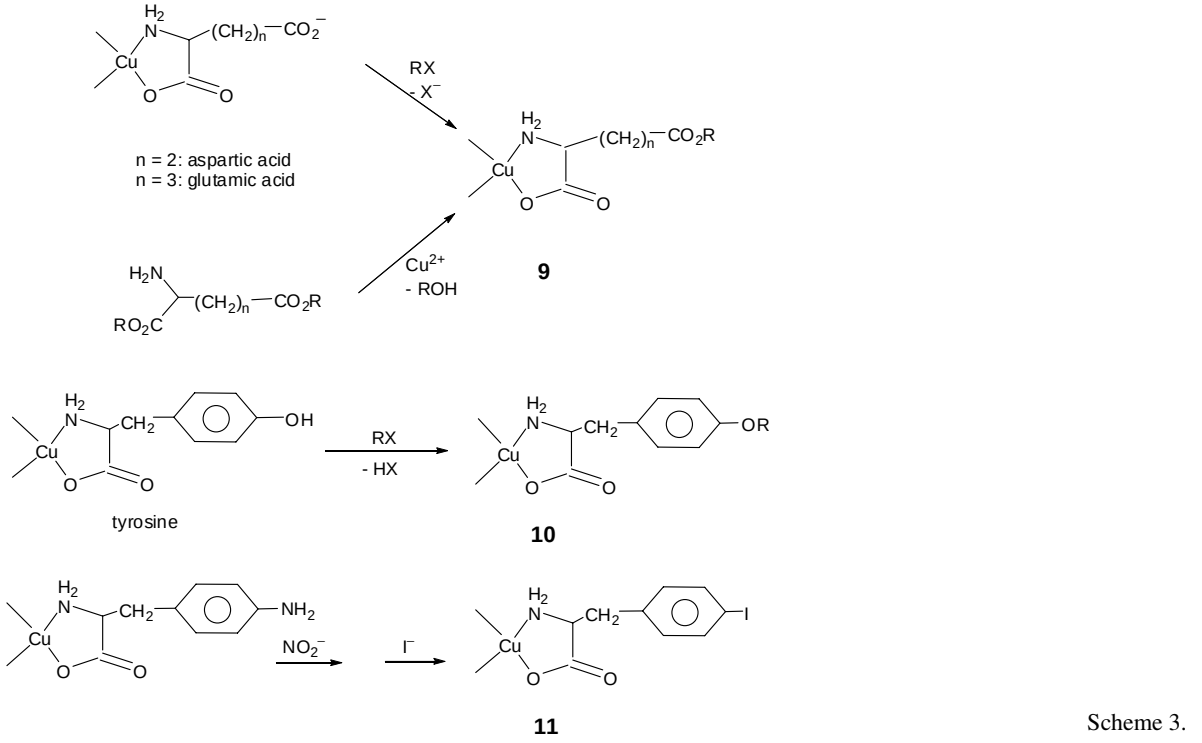
1.3. Copper(II) complex of tyrosine

The copper tyrosinate chelate complex with masked α-amino and carboxylic groups [91] was O-alkylated with acetic acid anhydride [92], with benzylchloroformate [93], with benzylbromide [94, 95], with 2,6-dichlorbenzyl bromide [25], with $BrCH_2C_6H_4Br$ [26], and *p*-$BrC_6H_4CONMe_2$ [96] to give **10** (Scheme 3). The *O*-alkylated (acylated) tyrosine **10** was used – after removal of Cu(II) – for the synthesis of polytyrosine [92, 93] and of several tyrosine derivatives [94 – 96].

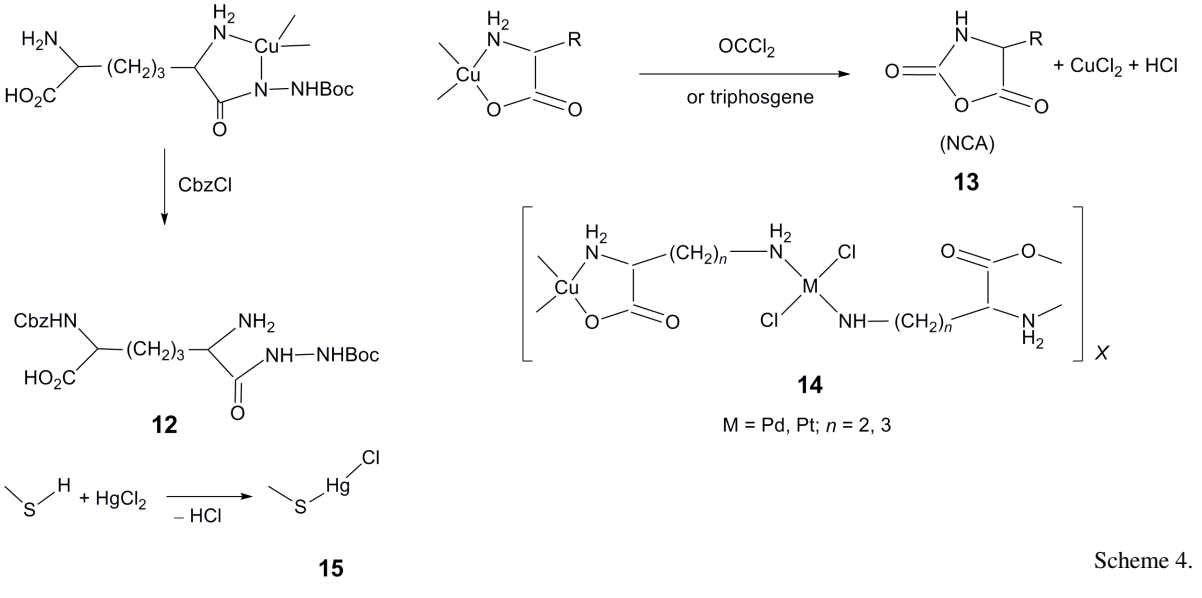
1.4. Several other applications of copper(II) complexes in amino acid chemistry

p-Iodophenylalanine was prepared from its copper complex **11** *via* the copper chelate of *p*-aminophenylalaninate which was converted into the diazonium salt and reacted with potassium iodide (Scheme 3). Copper(II) was then precipitated by H_2S [97].

A remarkable selectivity was observed for the carbobenzyloxylation of a diamino primelic acid derivative which contains a hydrazide group $H_2NC(H)$



Scheme 3.



Scheme 4.

(COOH)-$(CH_2)_3$-C(H)(NH_2)CONHNHBoc in the presence of copper(II) [3d, 98]. In the reaction with carbobenzoxychloride the Cbz-group was introduced into the glycine residue, and the other amino group was masked by Cu(II) to give CbzNHC(H) (COOH)-$(CH_2)_3$-C(H)(NH_2)CONHNHBoc (**12**). This observation demonstrates that the copper complex of the amino acid hydrazide is more stable than that of the amino acid itself, which may be due to deprotonation of the hydrazide function (Scheme 4).

Specific modification of the single lysine residue in glucagon with *O*-methylisourea has been effected by blocking the amino group of the terminal histidine with copper(II) to give homoarginine-glucagon [99]. *N*-Carboxy-α-amino acid anhydrides **13** (NCA, Leuchs anhydrides) were obtained in good yields by reaction of copper(II) α-amino acidates with phosgene [100] (Scheme 4). The copper(II) complex of lysinate was reacted with 9-fluorenylmethyl- and 6-nitroveratryl chloroformate, and the functionalized Cu(II) complexes were transformed with triphosgene into the corresponding NCAs. From these the N^{ε}-Fmoc and N^{ε}-Nvoc moieties could be cleaved with piperidine or by UV irradiation [101]. These lysine NCAs with labile side chain protective groups were copolymerized [101].

The copper complexes of diamino acids $H_2NCH(COOH)(CH_2)_nNH_2$ (n = 2, 3, 4) were reacted with *N*-carboethoxyphthalimide [57] to give **5** (Scheme 1), and the copper ion was removed with hydrochloric acid instead of hydrogen sulfide to give α-amino-ω-phthaloyl amino acids. Treatment with nitrous acid followed by removal of the phthaloyl group by hydrazine afforded the α-hydroxy-ω-amino acids $H_2N(CH_2)_nCH(OH)COOH$ (n = 2 – 4) [102].

1.5. Removal of copper(II) from functionalized amino acidate chelate complexes [4]

In the early applications of the "copper method" usually hydrogen sulfide has been used for the precipation of copper(II) as copper sulfide from the copper complexes. Many efforts have been undertaken to avoid H_2S. The H_2S method is often unsatisfactory, particularly in larger scale preparations [103 – 105]. Thioacetamide [38, 54, 106, 107] was used instead of the unpleasant H_2S [32]. Effective methods include the use of the "stronger" ligands cyanide [65 – 67, 71, 103] and (often and preferably) EDTA [25, 40, 41, 44, 52, 84, 86, 87, 104, 105, 108], and high yields were achieved [103 – 105, 108]. According to Stewart [105] and Bayer *et al.* [108] this EDTA method is advantageous where the solubility of the derivatives is poor or where the protecting groups are not stable in acidic conditions. In a series of studies an ion exchange resin was applied for the removal of Cu(II) [28, 73 – 76, 80]. The method with cyanide was introduced by Zahn [65, 71, 103], that with EDTA by Kuwata and Watanabe [104] and by Ledger and Stewart [84, 105].

Removal of copper from the N^{ε}-acyl-lysinate complex could be accomplished by 2-nitrobenzylsulfenyl thiocyanate [109]. The use of *N*,*N*-dialkyl-*N'*-(benzoyl)thioureas, *e. g.* $(n\text{-}C_4H_9)_2N\text{-}C(S)\text{-}N(H)COPh$, proved to be an effective method to decompose the copper complexes of copper-protected lysine, ornithine, glutamic acid and tyrosine [110]. A mixture of $MeSO_3H$ / CF_3COOH / PhSMe was used for the removal of copper from the N^{ε}-benzenesulfonyl-lysinate complex [56].

Improved methods for the synthesis of mono- and bis(alkoxycarbonyl) derivatives of lysine and ornithine were reported where 8-hydroxyquinoline was used for the removal of Cu(II) [29 – 32]. In some cases removal of Cu(II) was successful with hydrochloric acid [39, 58 – 60, 94, 102]. This was demonstrated for the copper complexes of *O*-benzyl-tyrosine [94], of N^{ε}-MZ-lysine [39] and N^{δ}-phthaloyl-ornithine, -lysine [58-60] and -diaminobutyric acid [102].

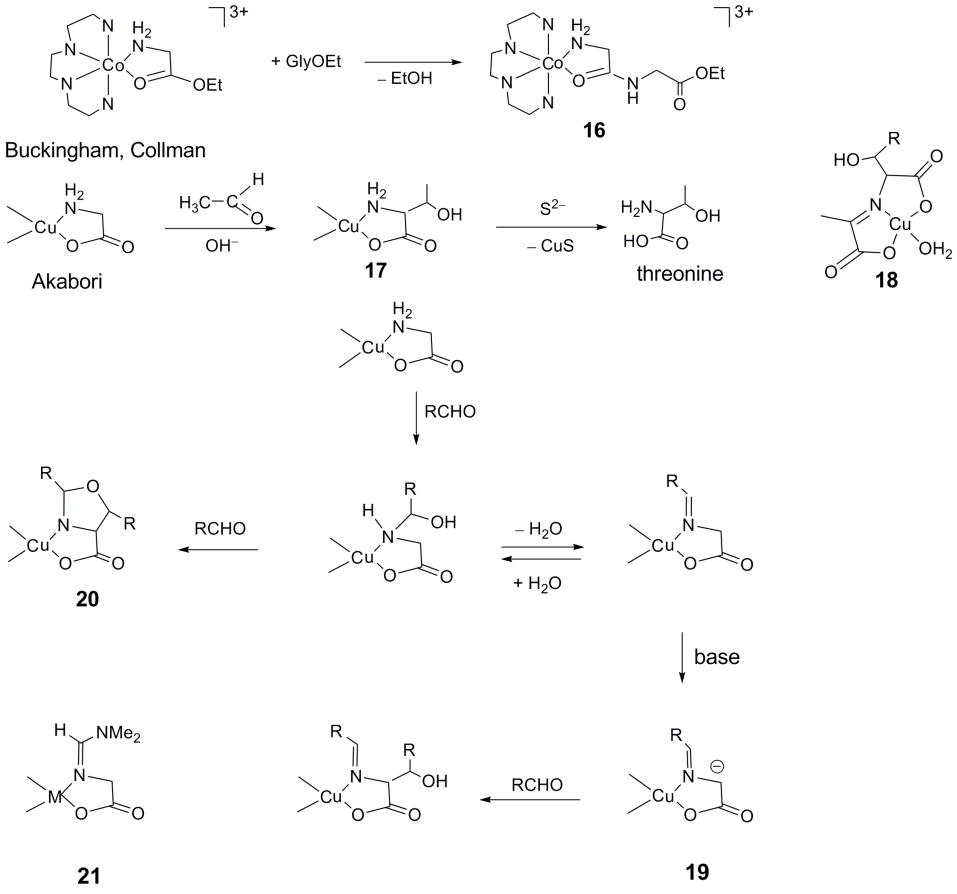
Recently the use of sodium sulfide [111] and of sodium tetrahydridoboranate (reduction of Cu(II) to copper(I) oxide as precipitate) [112] was demonstrated with many examples for the removal of copper from amino acid copper complexes. Both methods proceed with high yields at ambient temperature and without racemization, and thus appear to be attractive.

1.6. Coordination of the free ω-NH_2 group of lysinate and ornithinate complexes

N,*O*-Cu(II) complexes of lysine and ornithine react with K_2PdCl_4 or K_2PtCl_4 to give (presumably) the coordination polymers **14** [113] (Scheme 4). A dinuclear complex $Cp^*(Cl)Ir[NH_2CH(CO_2)(CH_2)_4NH_2]RhCl_2Cp^*$ could be detected by spectroscopic methods [114]. The coordination of the side chain NH_2 function in dipeptide Cu(II) complexes with lys-tyr [115] and gly-lys [116] was determined by X-ray diffraction and was also observed in solution [115]. Mass spectrometric evidence for the involvement of the lysine side chain in the coordination of the Zn(II) ion in enzyme model complexes was presented [117].

1.7. Protection of amino and hydroxyl groups by transition metal ions in amino glycosides and polyamines

Selective reactions of various amino groups in aminoglycosides have been achieved by temporary protection of vicinal and non-vicinal amino-hydroxy pairs with Cu(II), Co(II), Ni(II), and Zn(II) in aminoglycosides. This method which is important in the



Scheme 5.

chemistry of antibiotics has been reviewed [3d, 118]. Also selective reactions of polyamines in polyaza-macrocycles were possible [3d].

1.8. Protection of SH groups by Hg^{2+}

The thiol groups in cysteine-containing proteins have been reversibly protected by Hg^{2+} ions (**15**, Scheme 4) using $HgCl_2$, and the $HgCl^+$ protecting ions have been removed by H_2S (as HgS) [119], by a sephadex column [120] or by $NaBH_4$ (reduction to mercury metal) [121].

2. Metal Ions as Protecting Groups in Classic Coordination Complexes

This chapter deals with the reactions at coordinated amino acids. Competent reviews by Black [122a], Hay [122b], Gillard [123a], Pasini and Casella [123b], and Phipps [123c] have appeared.

2.1. Cobalt(III) complexes as amino-protecting and carbonyl-activating groups of α-amino acid esters

In 1967 Buckingham [124] and Collman [125] and their coworkers discovered the "cobalt(III)-promoted synthesis of small peptides" which combines amine protection with carbonyl activation of amino acid esters by Co(III). This discovery was made during attempts to prepare the Co(III) complex $[(trien)Co(GlyOEt)_2]^{3+}$ with two coordinated glycine residues [126].

The formed peptide can be liberated by reduction to labile Co(II), either electrochemically or with Hg/Zn. Also higher peptides could be prepared by the cobalt(III)-mediated synthesis [124] using repeated reactions of the amino acid ester cobalt(III) complex with peptide esters. The "Buckingham" chemistry – including the problem of racemization during peptide synthesis – has been reviewed in detail [126, 127]. An example (**16**) is given in Scheme 5.

Wu and Busch [128] studied the formation of peptide bonds at a three site Co(III) system using $[(dien)Co]^{3+}$ and succeeded in the preparation of the complex $[(dien)Co(glyglyglyglyOEt\text{-}2H^+]^+$ from $[(dien)CoCl_3]$ and glyglyOEt; *i. e.* the formation of a tetrapeptide by condensation of a (deprotonated) coordinated dipeptide ester with a free dipeptide ester was verified. See also refs. [129 – 132].

2.2. Reactions at the methylene group of N,O-glycinate chelate complexes

2.2.1. Reactions with aldehydes (Akabori reactions)

It is well established – from NMR studies of the exchange of α-CH_2 protons with D_2O – that N,O-coordination of α-amino acidates increases the acidity of the α-CH_2 bonds [133 – 140].

Akabori and coworkers [141] discovered the formation of β-hydroxy-α-amino acids by reaction of copper(II) glycinate with acetaldehyde to give **17** and threonine – after precipitation of copper as CuS (Scheme 5). This reaction has been used commercially for the production of threonine [142]. The aldol condensation of metal-coordinated glycinate can be performed also with other metal ions, *e. g.* with Co(III) [141b], Ni(II) [143], Pd(II) [144], and has found much interest [145].

In Schiff base complexes of α-amino acids and of peptides with pyruvate or salicylaldehyde, which – by the work of Snell *et al.* – show significant relevance with biological pyridoxal vitamin B_6 and its model complexes [146, 147], the nucleophilicity of the α-C atom is exhanced. The reactions of glycine Schiff base complexes with aldehydes to give *e. g.* **18** (Scheme 5) were actively studied by Harada [148], Nakahara [149] and Ichikawa [150, 151]. The higher activity of Schiff base complexes compared to bis(glycinato) copper complexes was also shown by reactions with sugar aldehydes [151], and an improved method for the isolation of hydroxyl amino acids by use of an ion exchange resin was presented [150 – 152].

Actually, the metal-catalyzed aldol addition of glycine with aldehydes was already discovered in 1953 by Metzler, Langenbecker and Snell [146]. They observed that the catalytic cleavage of hydroxyamino acids by pyridoxal and metal salts (Al^{3+}, Cu^{2+}, Fe^{3+}) is reversible, and they synthesized serine from glycine and formaldehyde, and threonine from glycine and acetaldehyde in the presence of pyridoxal and metal salts [146].

The mechanism of the reactions of metal glycinates with aldehydes was often discussed [122, 123, 143, 144, 150, 151, 153 – 156]. It is generally accepted that the initial attack of aldehydes at metal glycinates takes place at the amino group, and that a carbanion is the essential intermediate (Scheme 5), preferably of the imine complex **19** [150, 151, 156] (which is already present in the glycine Schiff base complexes). An oxazolidine complex **20** from the reaction of Cu(II) glycinate with acetaldehyde was first characterized by Pierrot and coworkers [157].

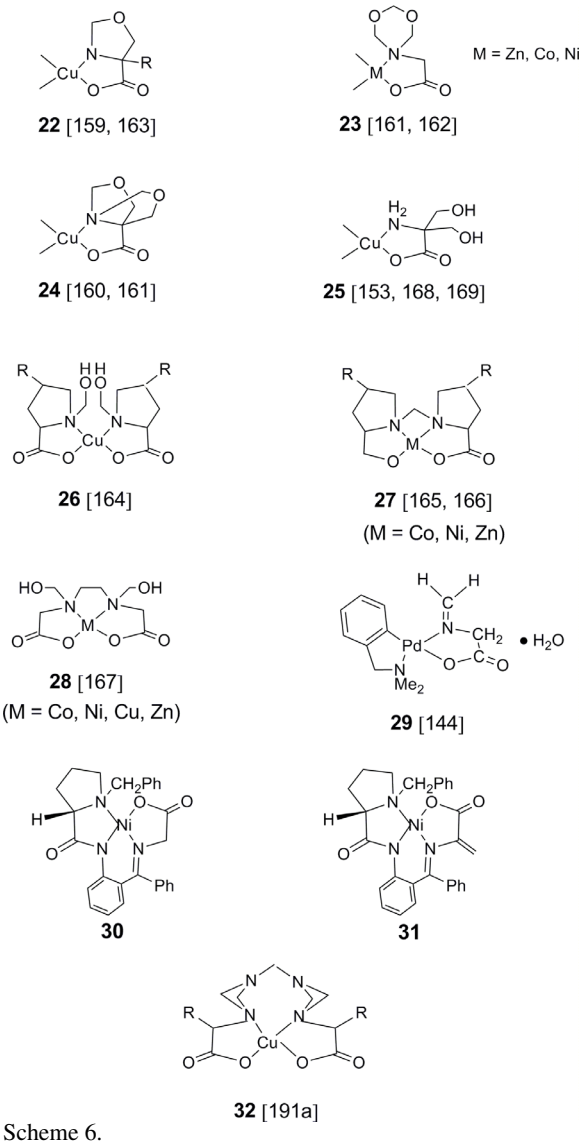
Various Schiff base complexes of nickel(II), cobalt(II), palladium(II) and platinum(II) and platinum(IV) of type **21** (Scheme 5) have been prepared from glycinato chelate complexes and dimethylformamide acetal [144].

In the Schiff base complex of glycinate with pyruvate the methylene group can be alkylated [149b] (see *e. g.* the O'Donnel reagent $Ph_2C{=}NCH_2CO_2Et$ or $Ph(H)C{=}NCH_2CO_2Et$ [158]).

The reactions of glycinato and other α-amino carboxylato chelate complexes with formaldehyde proceed quite differently from that with other aldehydes [153]. Practically all products which can formally be expected by addition of formaldehyde to the α-C atom and/or to the amino group of the *N*,*O*-chelate ligand to give hydroxymethyl species in the first step – followed by condensation of two hydroxymethyl groups – have been verified by Teo and coworkers [159 – 167], and the reaction path has been thoroughly studied by Casella, Pasini, and Ugo [153] (**22** – **28**, Scheme 6). The various products could be characterized by X-ray diffraction [160 – 167].

The end product of the reaction of *bis*(glycinato) copper with formaldehyde is – after removal of copper(II) – hydroxymethyl serine [153, 168, 169] with an oxazolidine complex as precursor [153], whereas the reaction of copper(II) glycylglycinate with formaldehyde afforded serylglycine as the main product [170]. The Co(III) complex $[(en)_2Co(\alpha\text{-hydroxymethylserinate}]^{2+}$ has been characterized by X-ray diffraction [171].

The product from the *ortho*-metallated *N*,*N*′-dimethylbenzylamine-glycinate Pd(II) complex with formaldehyde was formulated as the *N*-methylene Schiff base complex **29** (Scheme 6) [144]. Although the analysis for **29**·H_2O is identical with that for a serinate complex, evidence for **29** comes from the reaction of **29** with acetaldehyde which – after removal



Scheme 6.

of Pd(II) by reduction with H_2/Pd/C – afforded threonine [144]. Unexpected is the *N*,*N*′-dimethylation of Cu(β-alaO) by formaldehyde [172].

The Akabori reaction is a valuable method for new β-hydroxy-α-amino acids, *e. g.* β-hydroxyornithine or hydroxyglutaric acid as presursors for natural products [173, 174].

Of special interest are the many studies on the stereoselective formation of β-hydroxyamino acids. Two strategies can be recognized:

a) Chiral (optically active) glycinato complexes, *e. g.* $[(en)_2Co(glycinate)]^{2+}$, have been used [175, 176]; the origin of stereoselectivity was discussed by Phipps [123c, 177].

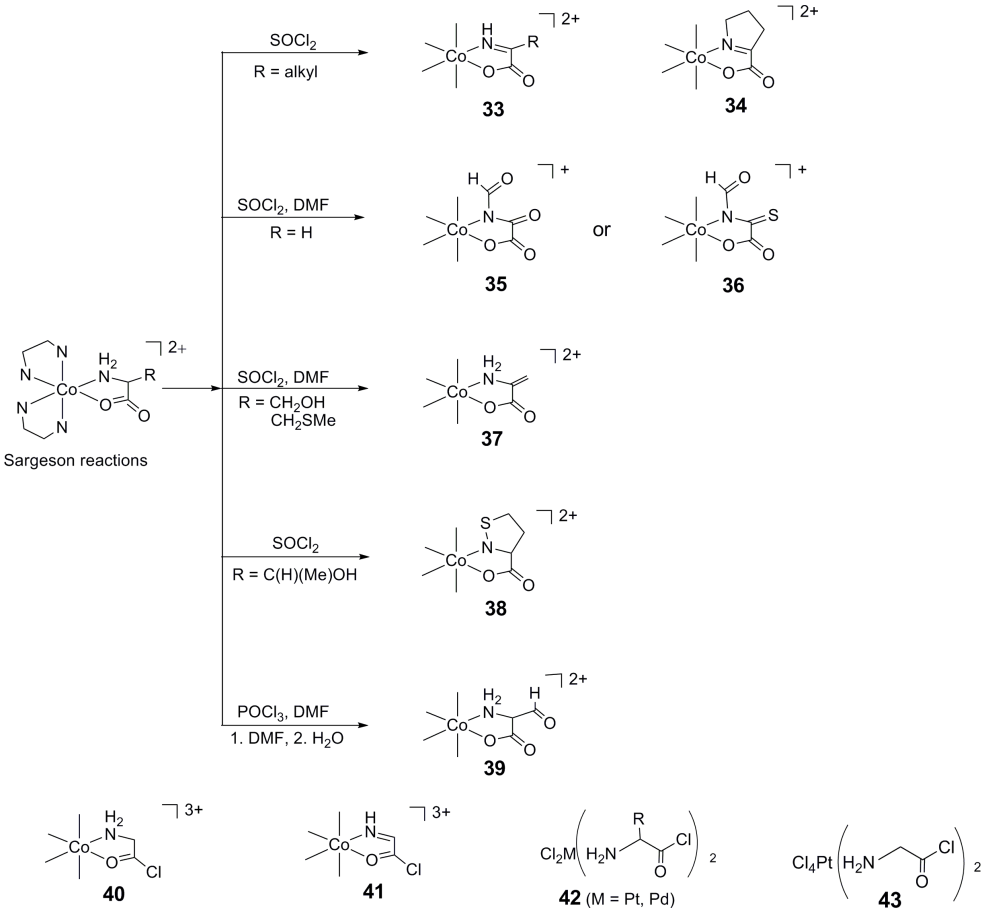
b) Very successful was the use of complexes of optically active glycine-containing Schiff bases, with dipeptides, *e. g.* of salicylaldehyde with glycyl-L-aminoacidates [178] or of pyruvate with glycine-D-phenylalaninate [179], or of glycyl imines of hydroxymethylene bornan-2-one for the synthesis of aromatic β-hydroxy amino acids [180]. For the latter reactions model studies for predicting the diastereoselectivity in the condensation of aromatic aldehydes with Zn(II) and Cu(II) Schiff bases have been reported [181].

In a large series of successful studies Belokon [143, 155, 182] and his school [183] used nickel(II) complexes of Schiff bases from glycine and optically active ketones for asymmetric aldol reactions with aldehydes. Especially with (*S*)- and (*R*)-*o*-[*N*-(*N*′-benzylprolyl)-amino]benzophenone (BPB) **30** (Scheme 6) [182] and its modifications [183] very high ee's could be achieved. Also asymmetric alkylations [183, 184] at the glycine moiety of these Schiff bases, diastereoselective Michael addition of the glycine residue to activated olefins [185], and asymmetric additions of radicals at the dehydroalanine residue **31** (Scheme 6) were studied [186]. The reaction of nucleophiles to the bromoglycinate Schiff base nickel(II) complex provides an asymmetric synthesis of α-substituted amino acids [187]. The asymmetric induction of the proline-containing Schiff base compares well with the role of proline itself as organocatalyst in asymmetric reactions [188] and with the diastereoselective formation of prolinato complexes which contain a chiral metal center [189]. It was attempted to use mixed glycinato-L-α-aminocarboxylato copper(II) complexes for stereoselective reactions with aldehydes [190].

Teo and coworkers reported a series of Mannich-type aminomethylation reactions of *bis*(aminocarboxylato) metal complexes with formaldehyde and ammonia or amides to give *e. g.* **32** [191] (Scheme 6).

Acrylonitrile was added to the amino groups of Cu(II), Ni(II) and Pd(II) glycinates; with *N*-salicylidene-glycinato copper(II) the two methylene hydrogen atoms were cyanomethylated [192].

In this context the [2+3]-cycloaddition reactions of imines from glycine and pyruvic acid or salicylaldehyde with olefins to give substituted prolines [193, 194a] may be mentioned. The catalytic formation of prolines from imines of α-amino acids

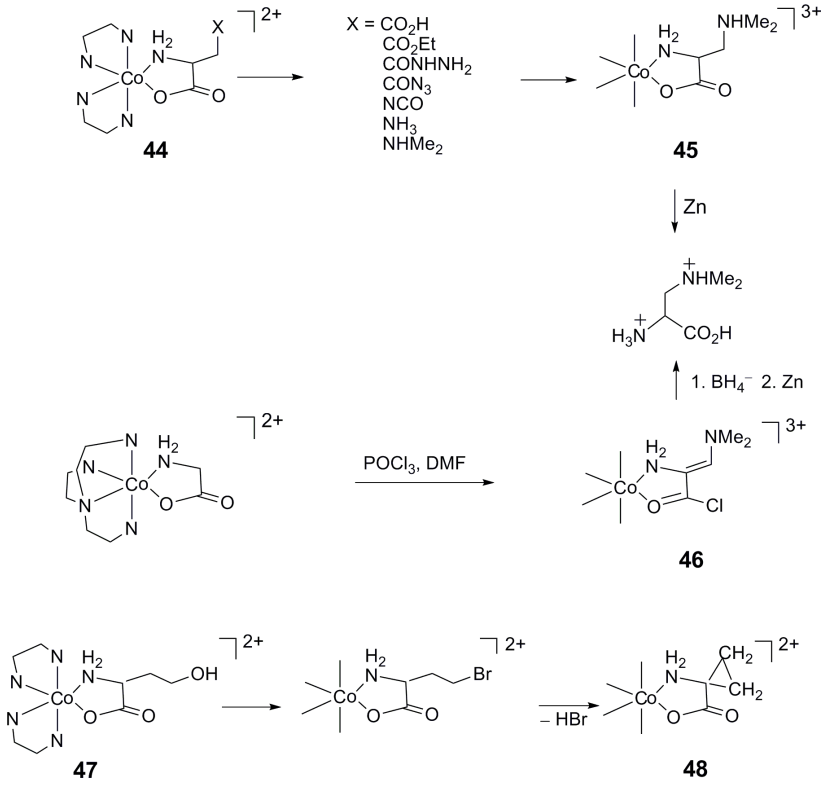


Scheme 7.

and olefins by 1,3-dipolar cycloaddition has recently been reported by Grigg [194b]. Also in the cyclopalladated complexes of Schiff bases from benzophenone and glycine, *e. g.* $(Ph_3P)(Cl)Pd[C_6H_4\text{-}C(Ph)=N\text{-}CH_2\text{-}CO_2R]$, the methylene group is activated [194c, 195], and their enolates can act as ambivalent 1,3-dipoles in [2+3]-cycloaddition reactions. A C-C coupling of the α-C atom of these enolates with π-coordinated hydrocarbons has been achieved [195c].

2.2.2. Reactions of (tetraamine)cobalt(α-aminocarboxylate) complexes with thionyl chloride and other "Sargeson" reactions

Sargeson and coworkers studied a series of interesting reactions at the *N*,*O*-coordinated α-amino acidates in which the metal ion plays a major role [196]. In the reactions of the chiral cobalt(III) complex $[(en)_2Co(\alpha\text{-aminoacidate})]^{2+}$ and [*tris*-(aminoethyl)amineCo(α-aminoacidate)]$^{2+}$ with thionyl chloride "the metal ion acts as protecting group and moderates the reactivity of the carboxylate and further, it activates the α-proton. Thus, the formation of the carbanion [133 – 140] and the attack by electrophiles is facilitated" [196]. From $SOCl_2$ and the complexes $[(en)_2Co(NH_2CH(R)CO_2)]^{2+}$ the α-imino acidate complexes **33** were obtained [196] (Scheme 7). Oxidation of the coordinated α-amino acidates by $SOCl_2$ occurs also with prolinate and picolinate to give *e. g.* the α-pyrroline carboxylate complex **34** [196]. Oxidation of proline to pyrroline-2-carboxylate has been observed also with the Pd(IV) complex $[PdCl_6]^{2-}$ to give [(pyrroline)(Cl)Pd(pyrroline-carboxylate)] [197]. Oxidation of Co(III)-chelated hydroxyl- and chloroprolines leads to pyrrole-2-carboxylate complexes [198]. Instead of $SOCl_2$ also a mixture of PBr_3 and *N*-bromosuccinimide was used for oxidation of chelated Gly, Sar, Ala and Glu to give the corresponding imine compounds $[(en)_2Co(HN=CH(R)CO_2)]^{2+}$ [199]. Yamaguchi *et al.* [200]



44 **45** **46** **47** **48**

Scheme 8.

synthesized iminocarboxylate cobalt(III) complexes by oxidation of *N*,*O*-chelates of aminocarboxylates with $KMnO_4$. Also other routes to imino carboxylate complexes are known [196, 200, 201].

The imino compounds can be reduced by dithionite and $NaBH_4$ to the starting amino carboxylate complexes [201, 202].

The reaction of the glycinate complex $[(en)_2Co(NH_2CH_2CO_2)]^{2+}$ with $SOCl_2$ in DMF afforded the *N*-formyloxamato complex **35** or – depending on the reaction conditions – the thioxamato complex **36** (Scheme 7) [203]. An *N*-methyl thiooxamato complex is formed from sarcosinate and $SOCl_2$ [204]. The reactions of the serinate and *S*-methylcysteinate complexes with $SOCl_2$ give chelated enamines **37** which rearrange to the imine complexes **33** [205]. The latter are formed also by base-catalyzed elimination reaction of coordinated *O*-acetyl and *O*-sulfonyl serine [206]. The threonine complex and $SOCl_2$ gave finally the 3-carboxyisothiazoline ligand **38** [205, 207]. Interestingly, the chiral *C*-formylglycinato complexes $[(en)_2Co(NH_2C(H)(CHO)CO_2)]^{2+}$ **39** and $[(tren)Co(NH_2C(H)(CHO)CO_2]^{2+}$ [tren = $(H_2NCH_2CH_2)_3N$] are formed by addition of the dimethyliminium species (formed from dimethylformamide and phosphorus oxychloride, Vilsmeier-Haack reaction) and subsequent hydrolysis [208 – 210]. The structure of the hydrated form of $\{(tren)Co(NH_2C(H)[C(H)(OH)_2]\}^{2+}$ was determined by X-ray diffraction [209]. In these reactions with $SOCl_2$ (or $POCl_3$) complexes with *N*,*O*-amino acid chloride **40** or imino acid chloride **41** were proposed as intermediates (Scheme 7). The structure of the (unhydrolyzed) Vilsmeier-Haack adduct, $\{(tren)Co[3$-(dimethylamino)-2-aminoacrylchloride]$\}^{3+}$ (**46**), was established by X-ray diffraction. Such complexes with amino-protected amino acid chlorides of platinum and palladium **42** and **43** could be isolated in our group (Scheme 7) [211 – 213].

The formyl group of **39** is reduced readily with BH_4^- to the serinato complex [208, 210], and condenses with penicillamine to give the corresponding Co(III) complex of the coordinated penicilloates in a stereoselective manner [210].

The oxidation of the *N*,*S*-bonded cysteinate $[(en)_2Cobalt(III)]$ complex with H_2O_2 afforded coordinated sulfinate and sulfinate in $[(en)_2Co\ cystSO]^{2+}$ and $[(en)_2Co\ cystSO_2]^{2+}$ [214]; the oxidation with chlorine leads to ring expansion and formation of

chelated sulfonate complexes $[(en)_2CoNH_2C(H)(COOH)CH_2SO_3]^{2+}$ [215], and the oxidation with Me_2SO / $(MeCO)_2O$ affords a sulfenamide complex (with participation of an amine ligand) [216a] which can be converted to an aminothiazoline complex [216b].

Another remarkable application of the $[Co(en)_2]^{3+}$ moiety as protecting group is the formation of 2,3-diamino propionic acid (4-azaleucine) at the Co(III) center [217]. The reaction sequence is shown in Scheme 8: asparaginate complex **44** (X = CO_2H) → asparagine ester (see section 1.2) → hydrazide → acylazide (Curtius rearrangement) → isocyanate → amine (**45**) → liberated 2,3-diaminopropionic acid. An alternative (achiral) strategy is provided by the reaction sequence at Co(III): glycinate (Vilsmeier-Haack) → 3-(dimethylamino)-2-aminoacryl chloride **46** → 2,3-dimethyl amino propionic acid.

The ripening agent 1-aminocyclopropane-1-carboxylic acid could be synthesized from the $[Coen_2]^{3+}$ complex **47** with homoserinate as ligand *via* the coordinated 2-amino-4-bromobutyrate to give **48**. The $[Coen_2]$ moiety acts both as amino-protecting and methine-activating group throughout the synthesis [218a] (Scheme 8).

Intramolecular condensation of an amino group of en with $Co(en)_2$-coordinated methyl methioninate finally gave the pentadendate ligand 1,9-diamino-4-hydroxy-3,7-diazanonane-4-carboxylate [218b].

2.3. Survey on the reactions of cobalt(III)-coordinated glycine

The robust tetraamine cobalt complexes $[(N)_4Co(glycinate)]^{2+}$ [N_4 = $(en)_2$, trien, tren] proved to be parade examples for reactions of the coordinated α-amino acids:

a) The methylene group of N,O-coordinated glycinate is activated by coordination and is susceptible towards attack by electrophiles (the Akabori reaction $[(en)_2Co(glycinate]$ with aldehydes is also known) [153, 163, 164].

b) Nucleophiles, *e. g.* α-amino esters, can attack the carbonyl group of the N,O-coordinated glycine esters to give a dipeptide [126]. The metal ion-catalyzed hydrolysis of α-amino acid esters follows the same mechanism [122].

c) The α-amino group of coordinated α-amino acids can act as nucleophile and can be attacked by organic carbonyl compounds to give a Schiff base, or an oxazolidine ring [153, 157, 159, 163], or with phosgene an oxazoline dione [100, 101].

In α-imino acids an "Umpolung" at the α-C atom is achieved, nucleophiles; *e. g.* the hydride anion (as BH_4^-) [202] or the nitromethanide anion, acetylacetone or dialkylmalonate [199, 219], are added to the α-C atom to give α-amino acids. A recent example [220a] is the synthesis of 2-(nitromethyl) ornithine: by reaction of $[(tren)Co(ornithinate)]^{2+}$ with $SOCl_2$/DMF the corresponding imine complex $[(tren)Co(HN{=}C(H)(CO_2)(CH_2)_3NH_3]^{3+}$ is formed; addition of nitromethanide affords the complex $\{(tren)Co[2\text{-}(nitromethyl)ornithinate]\}^{3+}$ from which the ligand could be released by reduction with ammonium sulfide. A versatile and efficient template synthesis for novel polyamines (*e. g.* iso-spermidine) has been developed [220b] which includes a) addition of the C nucleophile acetylacetone to the activated imine C atom, b) condenation of an amino group of the diamine ligand in $\{[H_2N(CH_2)_3NH_2]_2Co(HN{=}CHCO_2)\}^{2+}$ with the keto carbonyl group and finally, c) reduction with $NaBH_4$ and decarboxylation.

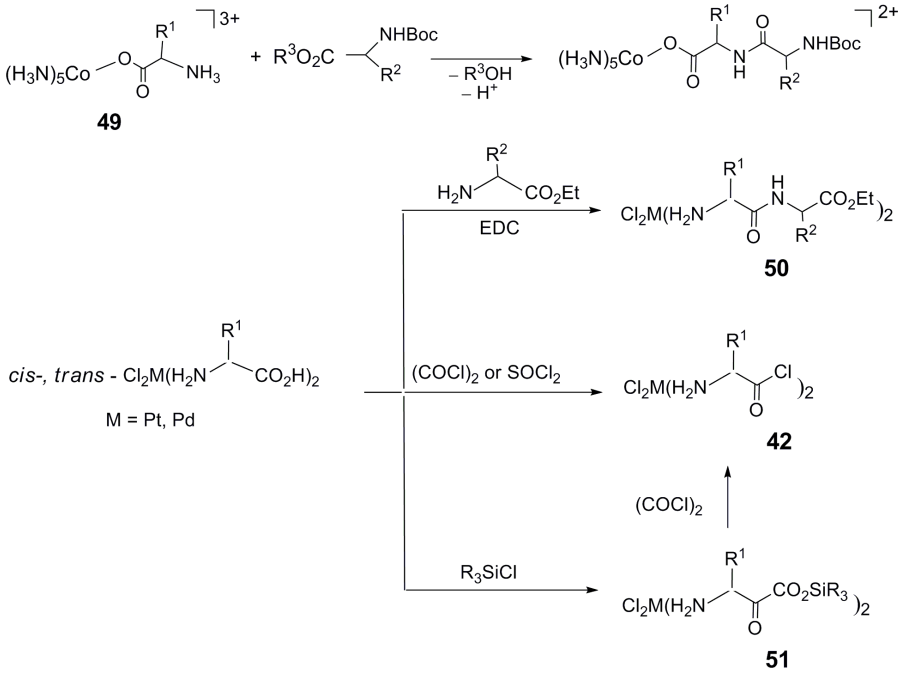
2.4. $[(H_3N)_5Co]^{3+}$ complex as carboxylate-protecting group

Isied and coworkers [221 – 226] introduced the pentaamine cobalt(III) complex **49** for the selective protection of the C terminus of α-amino acids in peptide synthesis (Scheme 9). This method has been successfully applied also by others [227, 228], *e. g.* for the synthesis of polylysine-based dendrimers with a $[Co(NH_3)_5]^{3+}$ at the core [229]. These complexes do not tend to racemize and are stable to CF_3CO_2H which is used to remove Boc groups.

This method has been applied in solid-phase synthesis of peptides [225, 226] using a complex $[(en)_2Co(p\text{-}aminomethyl\text{-}benzoate)(O_2CC(H)(R)NHBoc)]^{2+}$ which can be attached *via* the carboxylic group of benzoic acid to the aminomethyl polystyrene. The cobalt(III) protective group could be removed by reduction to labile Co(II) with NaHS or with $NaBH_4$.

2.5. Platinum(II) and palladium(II) as amino-protective groups

The concept to use platinum(II) or palladium(II) as effective amino-protecting groups was persued in our group in Munich [230]. The complexes *trans*- and *cis*-$Cl_2Pt(NH_2CHRCO_2H)_2$ with free carboxylic



Scheme 9.

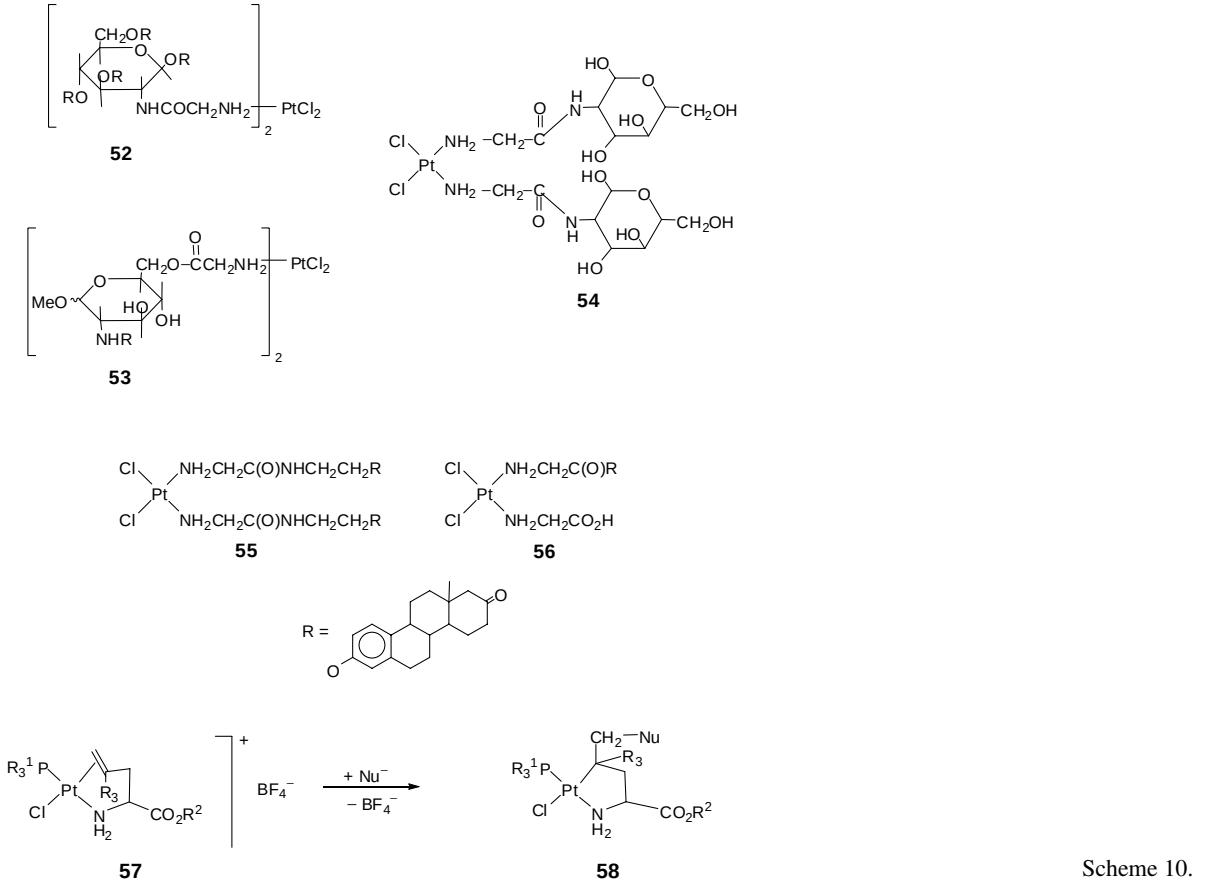
groups, first reported by Grinberg [231] and by Volshtein [232] (the pioneer in the chemistry of amino acid platinum complexes) have been used as starting compounds. The carboxylic groups of these complexes (which have been characterized by their IR spectra [233]) can be coupled with α-amino acid esters in the presence of coupling agents [234 – 238] to give **50**, whereby the water soluble *N*-ethyl-*N*′-[3-(dimethylamino)-propyl]carbodiimide ECD proved to be most suitable for peptide synthesis [238] (Scheme 9). Also a solid, polystyrene-supported carbodiimide has been used [236b]. Platinum(II) can be removed from dipeptide ester complexes by reduction to the metal with hydrogen or with $NaBH_4$ [238]. The pharmacology of *cis*-dichlorodi(peptide-ester) platinum complexes has been thoroughly studied [235].

The complexes $Cl_2Pt(NH_2CHRCO_2H)_2$ are easily converted to esters with alcohols in the presence of mineral acids [239 – 241] and form activated esters with substituted phenols from which various derivatives could be obtained under maintainance of the amino-platinum bond. Also the corresponding palladium complexes have been studied [213, 236]. The chelate ring of $Pt(glyO)_2$ is opened by acids or alkylating agents without cleavage of the (stable) amino-platinum bond [232, 239 – 241].

Even complexes with coordinated α-amino acid chlorides as ligands $Cl_4Pt(NH_2CHRC(O)Cl)_2$ (**43**) [211] and *cis*- and *trans*-$Cl_2M(NH_2CHR(O)Cl)_2$ **42** (M = Pt, Pd) [212, 213] could be isolated, *e. g.* from **51** (Scheme 9).

Starting from *cis*- and *trans*-$Cl_2Pt(NH_2CH_2COOH)_2$, Cl_2Pt(histidine), Cl_2Pt(methionine) various protected and unprotected monosaccharides, aminomonosaccharides, *e. g.* **52** – **54** (Scheme 10) [242, 243] and steroidal hormones [244] have been attached as esters or amides to platinum(II) through α-amino acid residues. 3-(2-Aminoethoxy)estrone, 3-(2-aminoethoxy)estradiol, 17-α-aminomethylestradiol and 3-ol-17-aminoestrane react with coordinated activated amino acid ligands of platinum(II) and palladium(II) complexes to give amino acid amide complexes *cis*- and *trans*-$Cl_2Pt(GlyNHR)_2$, $Cl_2Pt[(Gly)_nNHR]_2$ and Cl_2Pd-(HisNHR) (R = steroid, n = 1 – 3). Similarly, estrone, prednisolone, prednisone and testosterone have been bound in α-amino acid ester complexes *cis*-$Cl_2Pt(GlyOR)GlyOH$, *trans*-$Cl_2Pt(GlyOR)_2$ and $Cl_2Pd(HisOR)$ (R = steroid), *e. g.* **55** – **56** (Scheme 10). The aminoethyl-functionalized estrone *cis*-platinum complex **55** showed growth inhibition of MC-7 cells of the same order as "*cis*platin" [244].

The platinum(II) complex **57** with amino- and C=C-coordinated allyl glycine ester adds C nucle-



Scheme 10.

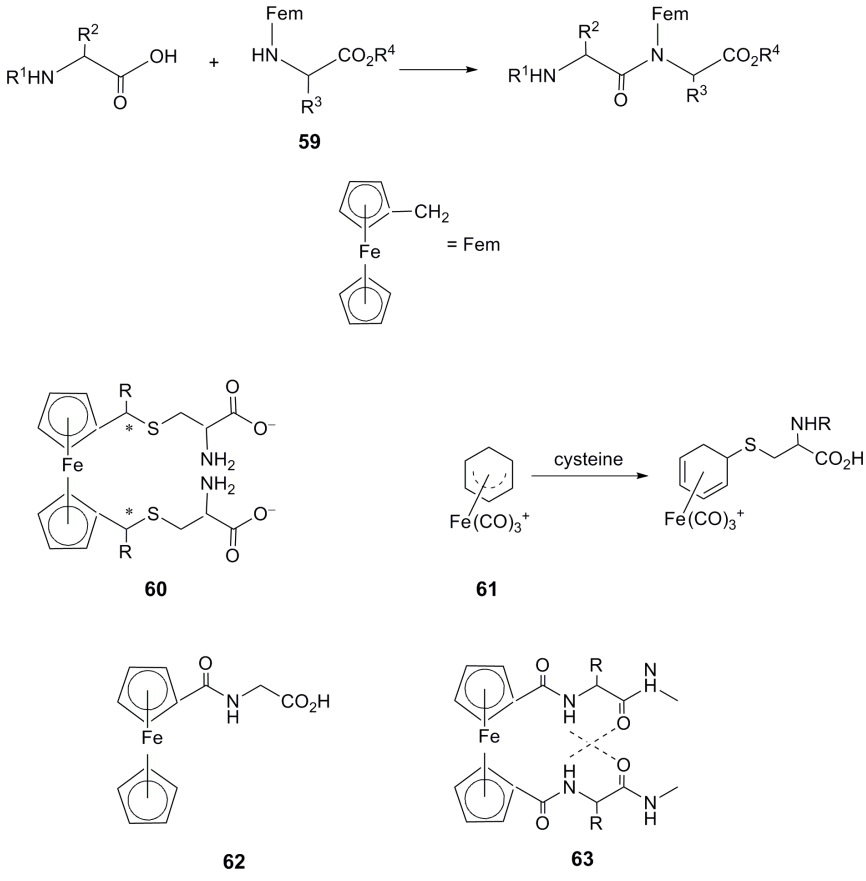
ophiles to give an interesting five-membered platina cyclus **58** (Scheme 10) from which by reaction with HCl and cyanide a novel α-amino acid could be obtained [245].

3. Organometallic Protecting Groups

The chromophoric and lipophilic ferrocenyl methyl residue (Fem), introduced by Eckert [246], permits the reversible masking of peptide bonds. The Fem group can be obtained without racemization by reaction of ferrocenyl aldehyde with α-amino acids, followed by catalytic hydrogenation with hydrogen [246]. The Fem amino acids **59** (Scheme 11) can then be coupled with amino-protected α-amino acids, and the Fem group can be cleaved by trifluoracetic acid. The advantages of this method have been summarized in ref. [3b,c]. Fem α-amino acid esters are available from ferrocene aldehyde and α-amino esters and subsequent reduction with $NaBH_4$ or $NaBH_3CN$ [247 – 250]. Metzler-Nolte and coworkers explored the peptide coupling synthesis with Fem amino acids [248 – 250].

The ferrocenyl methyl group has been successfully used for the selective protection of the thiol function, *e. g.* of cysteine, in the synthesis and labelling of glutathione [251, 252]. The Fem group can be easily introduced by reaction of cysteine with ferrocenyl methanol [253] in the presence of acid whereby the ferrocenylmethyl cation as active species [254] is added to the thiol group and can be selectively cleaved [251, 252]. Fem amino acids have been used as ligands in Pd(II) complexes [247], and the anions of ferrocenylmethyl-*S*-cysteine and ferrocenylenbis(methyl-*S*-cysteine) (**60**) (Scheme 11) have been proven as multidendate ligands to yield coordination polymers [255].

The cyclohexadienyl complex $[(\eta^5\text{-}C_6H_7)Fe(CO)_3]^+$ (**61**) has been shown to function as a novel and efficient SH protecting group which can be easily removed by trifluoracetic acid [256]. The cationic



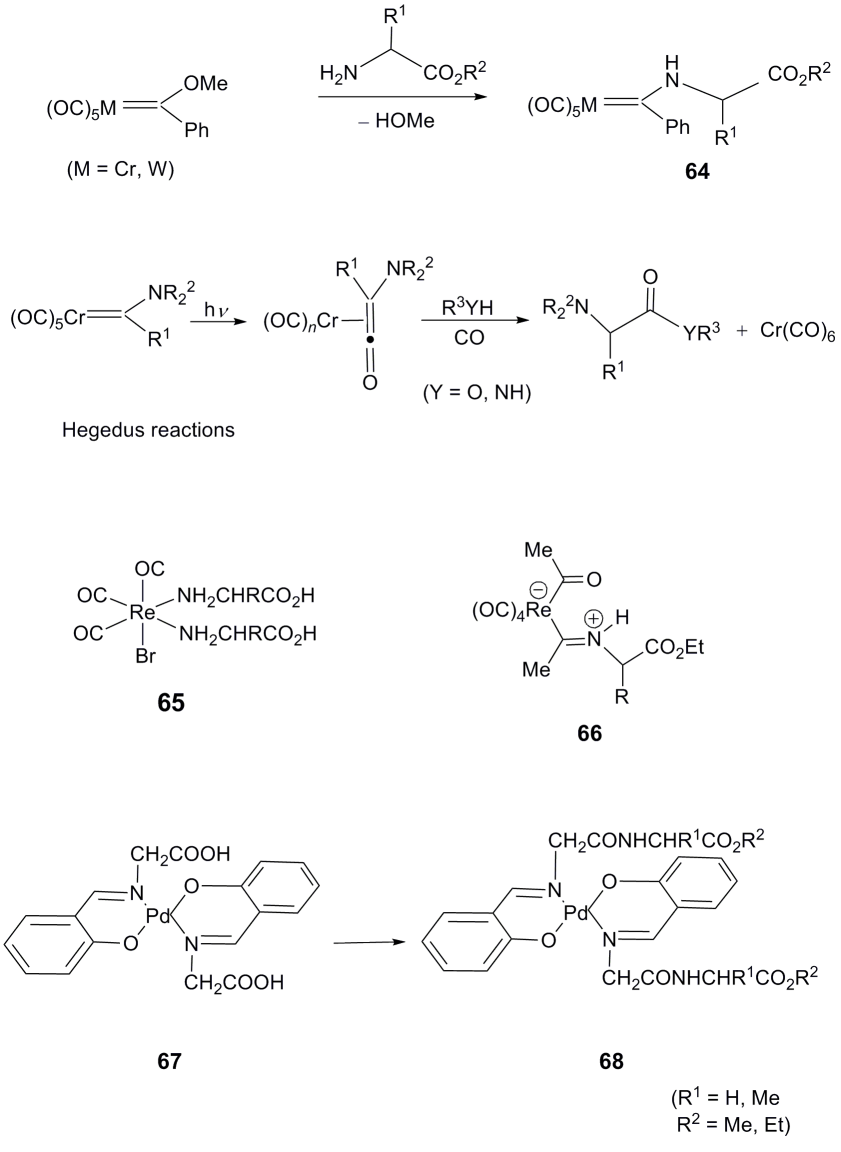
59 **60** **61** **62** **63**

Scheme 11.

dienyl complex $[(\eta^5\text{-}C_6H_7)Fe(CO)_3]^+$ shows a high affinity for the tertiary imidazole nitrogen of histidine, and adducts with a wide range of α-amino acid esters have been studied [257]. Analogous adducts of α-amino acid esters with $[(\eta^5(C_7H_9)Fe(CO)_3]^+$ and with [(allyl)(Cp)Mo(CO)(NO)]$^+$ have been obtained in our group [258].

A huge series [3c] of ferrocene derivatives with the ferrocenoyl moiety (the $CpFeC_5H_4CO$ moiety can be regarded as protective group) at the terminal NH_2 groups of amino acids and peptides (including hormones) have been obtained by Schlögl (**62**) [253] already in 1957, by Herrick [259], Hirao [260], Kraatz [261], Metzler-Nolte [249, 262] and their coworkers from ferrocene carboxylic acid or from ferrocenylcarbonyl-chloride. Especially the dipeptide derivatives of 1,1′-ferrocene dicarboxylic acid **63** (Scheme 11) found great interest because of their – through H-bonding – highly ordered structures between the two peptide chains [249, 259 – 263]. In our group ferrocene-1,1′-di(peptideesters) were obtained by reaction of ferrocene-1,1′-bis(oxazolone) with α-amino acid esters [264]. The ferrocene complexes with α-amino acids and peptides have been recently covered in a comprehensive and authoritative review by Metzler-Nolte and Salmain [249]. Peptide coupling synthesis was studied with ferrocenylmethyl (Fem) amino acids [248 – 250], with Mo(allyl)$(CO)_2$(R-hist) [265], with $(\eta^5\text{-}C_5H_4COOH)Mo(CO)_2$(allyl) [266b,c], with $CpFeC_5H_4COOH$ and $[CpCoC_5H_4COOH]^+$ [266b], with ferrocenyl benzoic acid $CpFeC_5H_4C_6H_5COOH$ [267a] and with $(OC)_3Mn(\eta^5\text{-}C_5H_4COOH)$ [267b] as labelling (protective) groups, using solution or solid-phase methods [249]. Alternatively, aminoferrocene has been attached to the *C* terminus of amino acids to give Boc-amino acid amides Boc-Aaa-NHFc [268].

The Fischer aminocarbene complexes $(OC)_5M{=}C(Ph)NHCH(R)CO_2Me$ (**64**) (M = Cr, W) with amino acid esters as amine component have been synthesized from the corresponding phenyl-methoxy-carbene compounds and have been used as amino-protecting

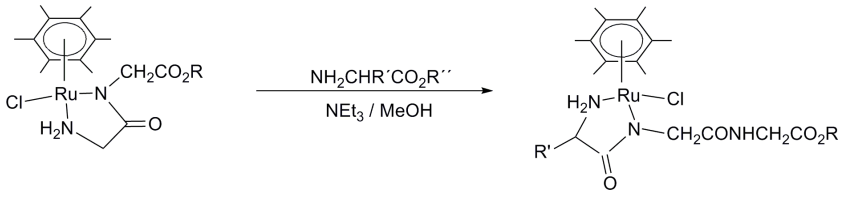


Scheme 12.

groups [269] (Scheme 12). The amino acid ester was hydrolyzed with NaOH, and the acid was activated and coupled with an α-amino acid ester. Tri- and tetrapeptides have been built up by this method, and the peptide can be removed by trifluoroacetic acid [269]. The Fischer method was extended with other functional amino acid esters (histidine, serine, lysine ester) and was used for the labelling of the free amino groups of lysine residues in the proteine bovine serum albumin [270].

A very interesting organometallic method for the synthesis of (optically active) α-amino acids and peptides was developed by Hegedus and coworkers [271]: The irradiation of Fischer aminocarbene complexes "drives a reversible insertion of one CO ligand into the metal carbon double bond" and the addition of alcohol or amines affords α-amino acid ester or amides, respectively (Scheme 12). In these reactions the $(OC)_nCr$ group can be regarded as protective group. More over, chromium hexacarbonyl could be recovered and reused in the presence of carbon monoxide [271].

The $Br(OC)_3Re$ moiety in *fac*-$Br(OC)_3Re(NH_2CHRCOOH)_2$ (**65**) (which is available from $Re(CO)_5Br$ and amino acid) was presented as a new protective group in peptide synthesis [272].



Scheme 13.

The rhenaacetylacetone $(OC)_4Re[C(CH_3)O]_2H$ was shown to condense with α-amino acid esters to afford the corresponding rhena-β-ketoimines $(OC)_4Re[C(O)CH_3][C(CH_3)=N\text{-}(CHRCO_2Et)(H)]$ (**66**) which can be hydrolyzed to rhena derivatives of the free acids from which the glycine derivative condensed with glycine ester to give the diglycine derivatives [273].

Schiff base palladium(II) complexes of amino acids (GlyOH, β-Ala, Phe) with free carboxylic groups have been obtained from Pd(salicylaldehyde-$H^+)_2$ [274] and amino acids [113, 275]. Coupling of **67** (Scheme 12) with amino acid esters by use of the water-soluble carbodiimide ECD afforded the corresponding dipeptide compounds **68**. However the ester groups could not be hydrolyzed (for further peptide formation) without decomposition [113].

The cationic acylium carbonyl-carbide-tricobalt cluster $[Co_3(CO)_9C\text{-}C{=}O]^+$, which is generated from the corresponding carboalkoxy compounds $Co_3(CO)_3C\text{-}C(O)OR$, has been proven as an organometallic acylating agent and forms amides with glycine ester and with peptides [276].

Outlook

In a forthcoming paper it is intended to give a short review on the "formation of peptides within the coordination spheres of metal complexes" (see *e. g.* refs. [125, 126, 128]).

In our group half-sandwich complexes of Rh, Ir and Ru have been used for a sequence-specific peptide synthesis [277] in which *N*,*N*′-coordinated peptides undergo selective chain lengthening at the N terminus by reactions with amino acids. An example is shown in Scheme 13. Also a metal-assisted template synthesis of cyclotetrapeptides at Cu(II), Ni(II) and Pd(II) centers from dipeptide esters has been developed in our group [278]. Both syntheses of peptides and cyclopeptides require neither activating reagents nor protecting groups.

It is the author's opinion that the expedition through coordination and organometallic chemistry keeping in mind how metal ions or metal complex moieties can act as protective groups has brought light to a series of interesting facts which may be stimulating for further research.

Acknowledgements

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