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Transition metal bioconjugates with an organometallic link between the metal and the biomolecular scaffold

Angèle Monney and Martin Albrecht

*School of Chemistry and Chemical Biology, University College Dublin, Belfield, Dublin 4,
Ireland.*

E-mail: martin.albrecht@ucd.ie; Fax: +353-17162501; Phone: +353-17162504.

Abstract

This overview compiles recent advances in the synthesis and application of organometallic bioconjugates that comprise a metal–carbon linkage between the metal and the biomolecular scaffold. This specific area of bioorganometallic chemistry has been spurred by the discovery of naturally occurring bioorganometallic compounds and afforded organometallic bioconjugates from transition metals binding to amino acids, nucleic acids and other biomolecules. These artificial bioorganometallic compounds have found application in various domains, including catalysis, medicinal chemistry, bioanalysis, and materials science.

Keywords: bioorganometallics, organometallics, bioconjugates, peptides, N-heterocyclic carbenes

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List of abbreviations

st	single stranded
ee	enantiomeric excess
Cp*	pentamethylcyclopentadienyl
Cp	cyclopentadienyl
Bz	benzoyl
Boc	<i>tert</i> -butyloxycarbonyl
cym	cymene
cod	1,5-cyclooctadiene
NHC	N-heterocyclic carbene
dmbipy	4,4'-dimethyl-2,2'-bipyridine

1. Introduction

Bioorganometallic chemistry in its broadest sense encompasses the chemistry of biomolecules and biologically active compounds that contain at least one carbon directly bound to a metal [1], hence lying at the interface of organometallic, medicinal and biochemistry. A wide array of naturally occurring bioorganometallic compounds have been identified in recent years, including cobalt, copper, nickel and iron systems [2]. Historically, B₁₂ coenzymes containing a cobalt–carbon bond have been the first organometallic species that were detected in natural systems (Fig. 1a) [3]. More recently, [FeFe]-, [NiFe]-, and the monometallic [Fe]-hydrogenases comprising CO and CN ligands directly bound to the iron centre(s) have been in the focus of synthetic chemists, in particular for mimicking Nature's efficient machinery to produce dihydrogen and to effectuate challenging reductions (Fig. 1b) [4].

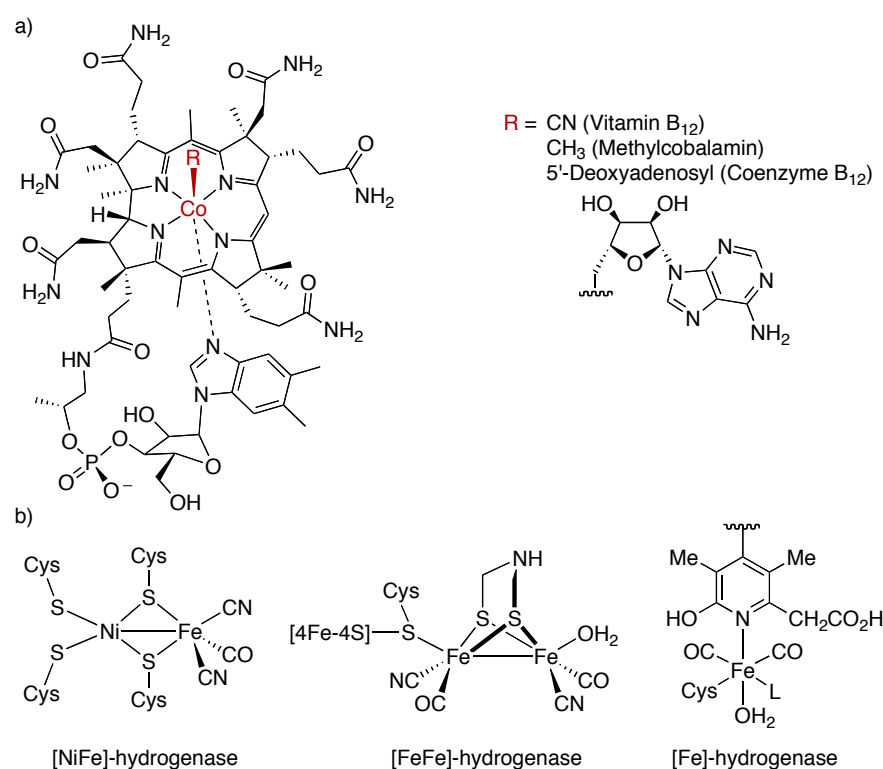


Figure 1 Examples of naturally occurring bioorganometallic entities featuring a) B₁₂ coenzyme and b) active sites of the three classes of hydrogenases.

The development of synthetic bioorganometallic chemistry has been greatly stimulated by these discoveries and also by the enhanced understanding of the metal–carbon bond paired with the substantial advances in spectroscopy, which allows metal bonding to proteins to be identified and characterised. In particular metal carbonyl complexes are highly suitable

synthons since biomolecules generally have an undisturbed spectral window at around 2000 cm^{-1} , a frequency where metal carbonyls feature intense $\nu(\text{CO})$ stretching bands [5]. Ferrocene constitutes another privileged synthon. Largely because of its numerous outstanding properties, ferrocene has spurred the development of modern organometallic chemistry in all its facets, ranging from homogeneous catalysis to materials science, and hence not surprisingly, also to bioorganometallic chemistry. The great stability of the ferrocenyl group in aqueous, aerobic media and its favourable electrochemical properties render ferrocene derivatives most popular for biological applications.

Initial progress in bioorganometallic chemistry has been slow. Organometallic complexes have long been assumed to be incompatible with water and oxygen and therefore unsuitable for combination with biomolecules. Only in the 1990s, bioorganometallic chemistry has started to attract more attention and has steadily grown ever since in different domains, such as in drug discovery, analytical chemistry, and catalysis [1,6].

The vast majority of synthetic bioorganometallic compounds developed thus far features a coordination bond between the biomolecule and the transition metal, and the bioorganometallic nature is entailed by spectator ligands, predominantly carbonyl or arene-derived π -bound ligands [7]. Thus, while the metal containing unit is organometallic, the metal–bioligand linker is not. Here we have compiled examples and applications of bioconjugates which specifically comprise an organometallic bond between the biomolecular scaffold and the transition metal, an area that has strongly profited from the discovery of formally neutral C-donor ligands such as N-heterocyclic carbenes [8]. This overview compiles the recent advances in artificial bioorganometallic systems with a particular emphasis on complexes containing a carbon-bound biomolecule in their first coordination sphere.

Of note, the wide field of bioorganometallic chemistry also includes “traditional” organometallic complexes that have a biological activity, and this specific area has particularly concentrated on potential applications in medicinal chemistry. Since the approval of cisplatin and related coordination complexes as anticancer drugs, research towards new organometallic compounds that avoid the serious side effects of these chemotherapy drugs has been greatly intensified [7,9]. Considering that most of these new antitumor-active complexes lack a biomolecular ligand, this area is not further treated here.

Nature provides a tremendous collection of chiral molecules, ranging from low molecular-weight amino acids and carbohydrates to macromolecules such as enzymes and DNA. These multifunctional building blocks bear great potential for the synthesis of organometallic

compounds, with applications in many areas, including medicinal chemistry, bioanalysis, materials science and catalysis. The increasingly growing research field of artificial bioorganometallic chemistry can be split into two main groups: organometallic complexes that bind to a macromolecule, such as enzymes and DNA, and metal complexes containing a small, well-defined biomolecule as a ligand, such as amino acids, carbohydrates, nucleic acids, steroids and oligopeptides.

2 Synthetic bioconjugates with a M–C bond to a macromolecular biological scaffold

The potential of bioorganometallic chemistry relies in part on the application of organometallic compounds in bioinspired catalysis, and especially in asymmetric catalysis. The use of macromolecules, such as enzymes and DNA, as ligands gives rise to organometallic complexes embedded in a chiral environment with both metal-based and biological properties. The different scales and often orthogonal analytical techniques used in the biochemistry of lipids, enzymes, and oligonucleoside chemistry on one side and on organometallic chemistry on the other provide distinct challenges in this area. Nonetheless, the promising results acquired thus far demonstrate great potential for further development.

2.1 Organometallic complexes with enzymes

Inspired by the natural (catalytic) activity of enzymes containing a metal centre in their active site, artificial metalloenzymes have attracted great attention as an approach to modify natural compounds for organometallic sensing, redox chemistry, and catalysis. The combination of an active organometallic moiety with a macromolecular host gives rise to functional entities possessing both homogeneous and enzymatic properties. The macromolecular scaffold provided by the enzyme allows for the recognition of small molecules that are transformed by the active metal site artificially embedded into the protein. Various strategies for the introduction of an organometallic unit with specific activity into a macromolecular host have been developed [10].

Early work focused on exploiting amide coupling strategies and involved acyl-functionalised ferrocene units as redox-active sites [11]. Decoration of various enzymes including galactose oxidase, streptavidin, and immunoglobulins has been demonstrated and provides biosensors with a distinct electrochemical response [12]. However, the number of covalently bound ferrocenyl units per protein is often only poorly controlled, which obviously hampers quantitative assays.

An alternative approach to the modification of metalloenzymes consists of the (covalent) binding of an organometallic moiety to specific amino acid residue containing reactive OH or SH groups [13]. For example, the holoprotein of azurin, a blue copper protein involved in electron transfer, has been functionalized with ferrocene through a disulfide linker (Fig. 2a) [14]. This link produces an artificial redox-active enzyme which features an iron rather than a copper centre in the active site. Building on this strategy, Hilvert and coworkers have introduced a cysteine residue into a 147 amino acid residue heat shock protein through a G41C mutation and subsequently appended a Grubbs-Hoveyda type olefin metathesis catalyst precursor via a bromoacetamide linker to this cysteine side chain (Fig. 2b) [15]. Modest catalytic activity has been observed in ring-closing metathesis under acidic conditions, though noteworthy, activities are in a similar order as those of the low-molecular and protein-free ruthenium complex.

Van Koten *et al.* have synthesised and crystallographically characterised lipases that are covalently modified by the insertion of phosphonate-pincer-metal complexes at Ser-120 (Fig. 2c) [16]. Transformation of the organometallic site has marked effects. For example, a μ -Cl bridged dimetallic system is obtained in chloride-poor buffer, thus effectively pairing up two lipase residues to give a quaternary structure that comprises two enzymes held together by a bridging chloride ligand. A similar reactivity has been previously established in unsupported pincer platinum chemistry.

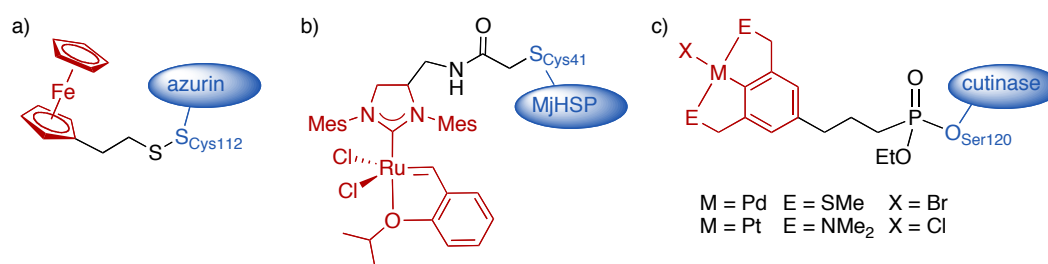


Figure 2 Organometallic complexes covalently bound to proteins: a) ferrocene [14]; b) carbene ruthenium complex appended a G41C mutant a small heat shock protein from *Methanocaldococcus jannaschii* (MjHSP) [15]; c) pincer platinum and platinum units immobilized at a serine residue of cutinase [16] .

Introduction of a pentaphenyl-substituted cyclopentadienyl ruthenium complex instead of a pincer moiety has been accomplished by the same synthetic trans-phosphorylation strategy at a lipase enzyme that catalyses enantioselective acylation reactions (CALB) [17]. The ensuing ruthenium lipase conjugate is a potentially bifunctional catalyst for racemisation (organometallic site) and enantioselective acylation (enzymatic site). Preliminary catalytic

tests suggest that the enzymatic activity is inhibited by the presence of the organometallic site. Fine-tuning of the immobilisation strategy and of the linker between the enzyme and the ruthenium centre may alleviate these limitations.

Substantial advances have been accomplished by exploiting the high non-covalent affinity of an inhibitor for a protein to introduce an organometallic moiety within an enzymatic environment. The biotin–(strept)avidin technology has been pioneered by Wilson and Whitesides [18] and relies on the extraordinarily high binding constant of biotin to (strept)avidin (dissociation constant $K_d \sim 10^{-14}$ M). Covalent modification of biotin with a chelating diphosphine Rh(I) complex affords a catalytically active artificial enzyme for the hydrogenation of α -acetamidoacrylic acid to *N*-acetylalanine, albeit with moderate enantioselectivity. Ward *et al.* have further developed this approach for various catalytic applications [19]. The artificial metalloenzymes can be optimised chemically by varying the biotin moiety and the spacer length, and genetically by mutation of the (strept)avidin host (Fig. 3). Various (strept)avidin–biotin–ML_n conjugates have been synthesised and tested as catalysts for different reactions, including ruthenium-catalysed hydrogenations, vanadium-catalysed oxidations, and palladium-catalysed allylic alkylations [19]. While these examples all feature a phosphine or amine/amide end-capped biotin, thus comprising a coordination bond between the metal centre and the donor-functionalised biomolecule, these studies unambiguously demonstrate the wide tolerance of a biomolecular scaffold to a variety of rather forcing reaction conditions. Inspired by these results, a second generation Hoveyda-Grubbs catalyst has been functionalised at the imidazolinyldene C4 position with a biotin anchor, thus providing an organometallic linker between the biochemical ligand and the metal centre. This biotinylated C-bound ruthenium complex has been embedded into the (strept)avidin binding pocket, thus affording an artificial metalloenzyme that catalyses ring-closing metathesis [19d] The spacer between biotin and the carbene ruthenium active site has a pronounced impact on the catalytic activity, in particular when using streptavidin as a host.

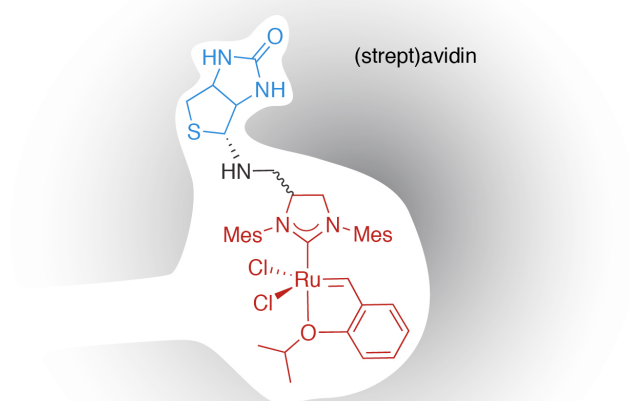


Figure 3 Schematic view of an artificial metalloenzymes for catalytic olefin metathesis based on the biotin–(stept)avidin technology [19d].

As an intrinsic advantage of using enzymes for the synthesis of bioorganometallic compounds the biomolecular scaffold can be modified by direct evolution. Protein engineering has hence emerged as a powerful technique for tailoring enzyme activities. Artificial amino acids can be introduced into the protein at specific locations, which greatly expands the possibilities for subsequent metal anchoring and for catalytic application of such artificial metalloenzymes [20].

2.2 Organometallic complexes with DNA

The utilisation of DNA as a ligand scaffold has been well explored in coordination and supramolecular chemistry [21], though DNA has been only little explored for organometallic linkages. This fact is rather surprising when considering that derivatives of adenine for example can bind metal centres through carbon (see section 3.2). Significant progress has been accomplished through the functionalisation of peptide nucleic acid (PNA), a DNA analogue based on a glycine backbone rather than a ribose phosphate skeleton, which binds complementary DNA single strands. Terminal or backbone functionalisation of PNA with ferrocenyl groups has been widely studied [22] and has been employed, for example, for the selective detection of specific DNA and hormones, and for the fabrication of an electrochemical immunoassay for protein kinase activity [22c]. Recent expansion of this technology includes ruthenocene PNA bioconjugates, which reveal a high cellular uptake and

better stability than ferrocene analogues [22e]. These properties together with the lack of a natural background of ruthenium are attractive attributes for further developments.

Jäschke and coworkers have introduced a chiral diene to an oligodeoxynucleotide by covalent anchoring (Fig. 4) and have combined this modified nucleotide sequence with different complementary DNA strands [23]. Addition of iridium has been assumed to afford new DNA-supported diene complexes that are active catalysts in allylic amination reactions. High yields and turnover numbers have been obtained, but the enantiomeric excess is consistently low, possibly because the iridium-olefin bond is not persistent in the catalytic cycle. Alternatively, the catalyst activation may be faster than the ligand exchange. Clearly though, DNA-based organometallic catalysis is underdeveloped and holds great promises.

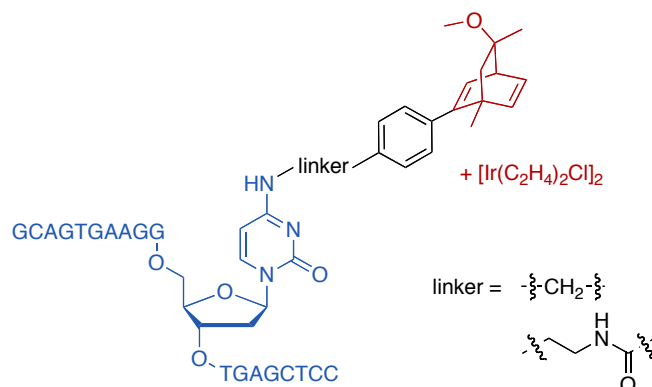


Figure 4 Diene-functionalised DNA for anchoring of metal complexes to DNA [23].

3 Bioorganometallics with low molecular-weight biomolecular scaffolds

The use of natural macromolecules such as proteins and DNA is an attractive new approach to asymmetric catalysis. However, a control over the positioning of the catalytic site(s) and therefore a precise characterisation of the species is generally difficult, often preventing a rational design of the catalysts. This disadvantage can be circumvented by using a bottom-up approach where smaller natural molecules are used as building blocks for the synthesis of ligands. Amino acids, carbohydrates, steroids, alkaloids and small peptides are some representatives of the large variety of chiral and multifunctional molecules which have been used for the synthesis of bioorganometallic compounds and that are easily available from nature.

3.1 Organometallic complexes derived from steroids

In 1985, Jaouen *et al.* have reported the first steroid-based organometallic complexes, a cornerstone that is often referred to as the beginning of synthetic bioorganometallic chemistry. Chromium tricarbonyl arene complexes of estradiol derivatives have been prepared and their potential application as IR probes in the diagnosis of hormone-dependent cancers has been targeted [24]. Later, this methodology has been extended to the synthesis of estradiol-based $\text{Ru}^{\text{II}}(\text{Cp}^*)(\text{Ar})$ and $\text{Rh}^{\text{III}}(\text{Cp}^*)(\text{Ar})$ complexes (Ar = estradiol derivatives) and their electrochemical behaviour has been investigated for potential application in metalloimmunoassay (Fig. 5a) [25]. Related $\text{Ru}^{\text{II}}\text{Cl}_2(\text{cym})$ complexes with *N*-coordinated estrogen and androgen isonicotinates are cytotoxic to hormone-dependent and hormone-independent cell lines (Fig. 5b) [26]. Ruiz and co-workers have functionalised levonorgestrel with an acetylene-linked phenylpyridine group. The corresponding cyclometallated $\text{Ru}(\text{II})$ complexes show higher antiproliferative activity than cisplatin towards breast cancer cells (Fig. 5b) [27].

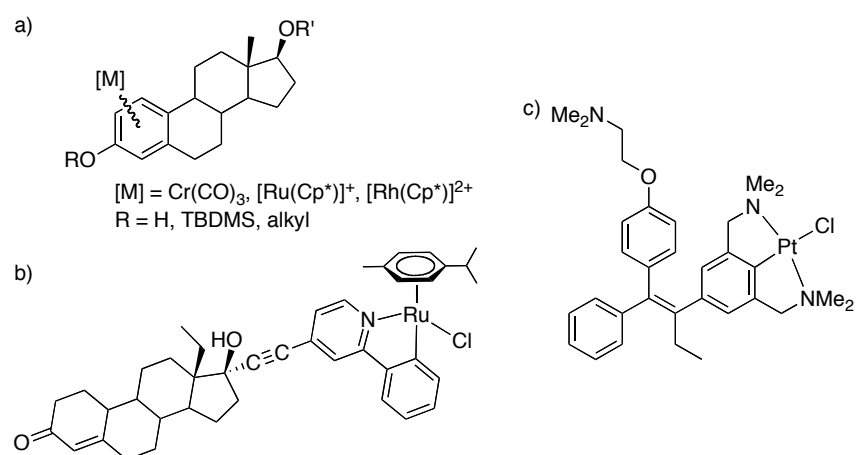


Figure 5 Organometallic complexes with steroids (TBDMS = $\text{Si}t\text{BuMe}_2$) [25-28].

Along similar lines and inspired by Jaouen's hallmark synthesis of ferrocifen [1], tamoxifen as a potent selective estrogen receptor modulator has been modified with robust NCN pincer platinum sites (Fig. 5c) [28]. The Pt–C bond in these metallacycles is robust under physiological conditions and may thus reduce cytotoxic side-effects during transportation to carcinogenic cell lines. In addition, a ferrocene derivative of estrone, ferrocenestrone, has been prepared recently in more than 15 steps [29]. This lengthy synthetic procedure constitutes a serious drawback for applying such organometallic conjugates in medicine.

3.2 Organometallic complexes derived from alkaloids and nucleobases

Xanthine derivatives have attracted attention for the synthesis of alkaloid-based carbene–metal complexes. The presence of an imidazole moiety in the structure of xanthines makes them valuable candidates for the synthesis of N-heterocyclic carbene (NHC) complexes. In 1975 Taube *et al.* have reported the first synthesis of xanthinylidene ruthenium complexes showing the strong *trans* influence of the carbene ligands compared to their *N*-bound analogues [30]. This bonding mode is further enforced when adding a chelating tether as demonstrated for a formal tautomerisation of adenine and guanine to induce *C*-bonding to a ruthenium(II) centre (Fig. 6a) [31]. When starting from a xanthinium salt rather than neutral xanthine, a similar carbene bonding is accomplished by proton abstraction. Accordingly, N-heterocyclic carbene rhodium and iridium complexes derived from alkylated caffeine (1,3,7,9-tetramethylxanthinium salt) have been synthesised independently by Youngs [32] and Herrmann [33], demonstrating the easy accessibility of imidazolylidene complexes from these precursors. Additionally, Cannon and Youngs have investigated xanthinylidene silver complexes for antimicrobial applications (Fig. 6b) [34]. *In vitro* and *in vivo* studies have revealed excellent efficacy of these complexes on some resistant pathogens. More recently, caffeine-based NHC palladium complexes have been successfully used as catalysts in cross-coupling reactions in aqueous solution [35], demonstrating the vast opportunities arising from the use of easily available natural products. Caffeine-based NHC platinum complexes are photoluminescent [36]. A significant impact has been attributed to the NHC ligand since the emission quantum yield is considerably lower than that of a related carbene-free platinum(II) complex.

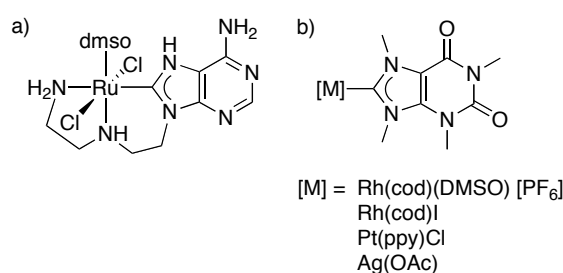
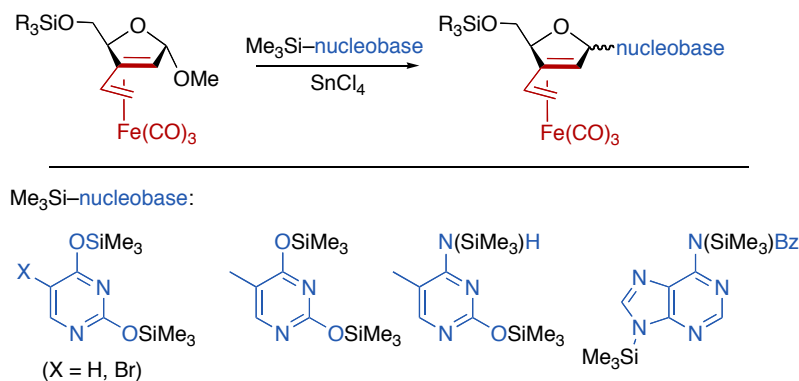


Figure 6 Organometallic complexes derived from a) adenine [31] and b) from xanthine [32–34] (ppy = 2-phenylpyridyl).

In complementary work, Schmalz and coworkers exploited the binding affinity of iron(0) to dienes to synthesise organometallic conjugates of nucleobases (Scheme 1) [37]. A variety of functionalised and natural nucleobases have been coupled to the Fe(diene) unit. The ensuing complexes are cytotoxic against tumor cells and induce programmed cell death (apoptosis)

through DNA fragmentation. Mechanistic work has demonstrated an essential role of the $\text{Fe}(\text{CO})_3$ fragment for the biological activity, as decomplexation results in a loss of the antiproliferative properties [37].



Scheme 1 Synthesis of $\text{Fe}(\text{CO})_3$ functionalised nucleobase conjugates [37].

Complementary to the ribose-type bonding of the iron(0) centre in the $\text{Fe}(\text{CO})_3$ complexes, ferrocene can be attached directly to the nucleobase through a benzylic linker (Fig. 7). Cytosine and uracil conjugates have been prepared according to these methodologies [38]. The ferrocenyl cytosine complex shows antitumor activity ($\text{LD}_{50} \sim 10 \mu\text{M}$) by inducing apoptosis in vitro in different cell lines of leukaemia and lymphoma, provided the substituent R is lipophilic (R = *t*Bu, silyl ether). Hydrophilic substituents (CH_2OH) or the exchange of cytosine for uracil leads to inactive complexes [38a].

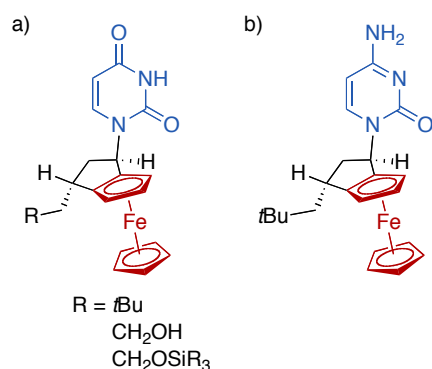


Figure 7 Nucleoside-functionalised ferrocene complexes containing a) cytosine and b) uracil as nucleobase [38].

Progress has also been achieved in preparing organometallic derivatives of platensimycin, a potent natural antibiotic. Half-sandwich complexes with $\text{Mn}(\text{Cp})(\text{CO})_3$ and $\text{Cr}(\text{arene})(\text{CO})_3$ and ferrocene-type iron(II) complexes have been prepared that structurally mimic natural platensimycin (Fig. 8) [39]. While the antimicrobial activity of these complexes against

Gram-positive and Gram-negative bacteria were surprisingly low, the lipophilic complexes display interesting cytotoxic activity against mammalian cancer cell lines.

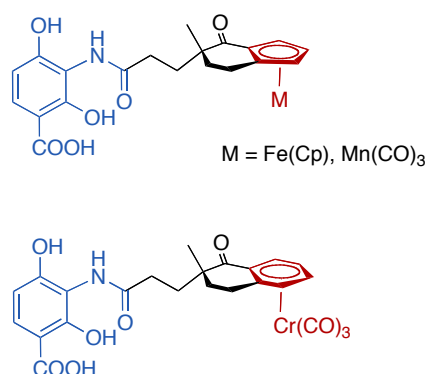


Figure 8 Organometallic bioconjugates derived from platensimycin [39].

3.3 Organometallic complexes with carbohydrates

Carbohydrates are a popular source of chirality and have been exploited as starting material for the synthesis of ligands for transition metals. Most carbohydrate-based ligands are derived from xylose, fructose, glucose, mannose, and tartaric acid and have been functionalised with donor atoms such as P, N and S for metal binding [40]. Carbohydrate-derived monodentate and bidentate P-based ligands including phosphines, phosphinites, and phosphites are most commonly used in asymmetric catalysis and have been demonstrated to induce high ee's in various reactions such as hydrogenations, hydroformylations, allylic substitutions, and 1,4-additions [40].

Only a small portion of carbohydrate-based transition metal complexes involves a direct C–M linkage to the sugar moiety. By far the most developed class of compounds is based on ferrocene-tagged carbohydrates, which have found application as biosensors and anticancer agents [41]. Investigations have been greatly stimulated by the discovery of ferroquine as organometallic antimalaria drug [42]. Indeed, a range of carbohydrate ferrocene conjugates display appreciable activity against malaria (Fig. 9) [43], which will undoubtedly further promote research in this area of bioorganometallic chemistry [44].

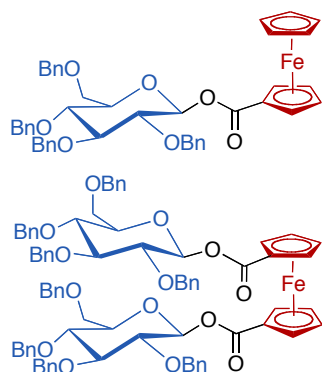


Figure 9 Carbohydrate ferrocene conjugates with antimalarial activity [43].

Dötz and co-workers have developed different strategies to prepare Fischer-type carbene complexes from cyclic and acyclic carbohydrates [45]. Thus, reaction of metallate anions with carbohydrate acid chlorides or lactams, olefin metathesis, cyclisation of alkynols, and addition of lithioglucals to metal carbonyls constitute successful methodologies for binding W, Fe, or Cr centres directly to a carbohydrate carbon atom. Interestingly, the presence of a metal fragment does not significantly affect the conformation of acyclic sugar skeletons. These carbohydrate-based carbene complexes exhibit characteristic properties of Fischer-carbene complexes and undergo typical reactions such as benzannulations and homologisation. Building on these results, amphiphilic organometallic complexes have been prepared by modifying an acyclic glucose-derived chromium pentacarbonyl carbene complex with a long alkyl chain followed by the deprotection of the glucose moiety (Fig. 10a) [46]. This organometallic complex gels thermoreversibly CHCl_3 and mixtures of CHCl_3 with benzene or toluene.

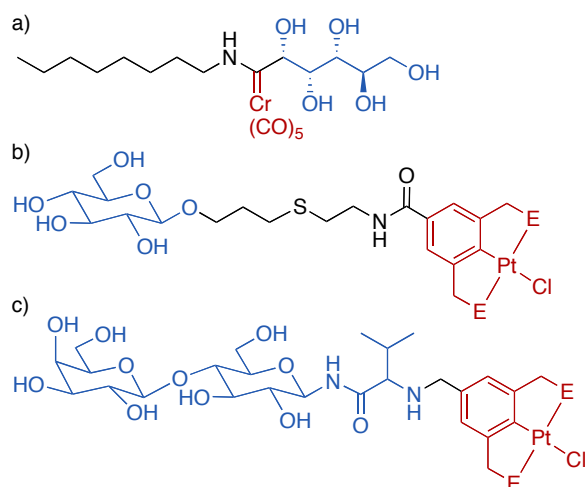


Figure 10 a) Chromium carbene carbohydrate conjugate as a gelator [46]; b) pincer platinum glucose conjugate [47]; c) pincer platinum lactose conjugate for biosensor signal enhancement [47].

Van Koten and co-workers have substituted glucose, galactose, and lactose covalently at the anomeric carbon with a NCN pincer platinum residue (Fig. 10b, c) [47]. These hybrids have been applied for surface plasmon resonance (SPR) signal enhancement and to assay carbohydrate–protein interactions. Control experiments have revealed that the SPR response is substantially improved with the pincer platinum aglycon, suggesting the bioorganometallic system to be an excellent label for signal amplification in biosensors.

More recently, carbohydrates have been decorated with N-heterocyclic carbene ligand precursors. Glucopyranosyl-substituted imidazolium salts have been successfully metallated *via* formation of a silver carbene intermediate and subsequent transmetallation. Almost simultaneously, Nishioka and Kinoshita have prepared an iridium(III) complex (Fig. 11a) [48], Glorius and coworkers have synthesised a bis(carbene) palladium(II) complex [49], and Shi *et al.* succeeded in rhodation of a carbohydrate-functionalised N-heterocyclic carbene precursor [50]. The rhodium complex comprised glucopyranose wingtip groups on both sides of a saturated carbene ligand, and complexation has been achieved in a base-mediated reaction using NaOtBu in the presence of [Rh(cod)Cl]₂.

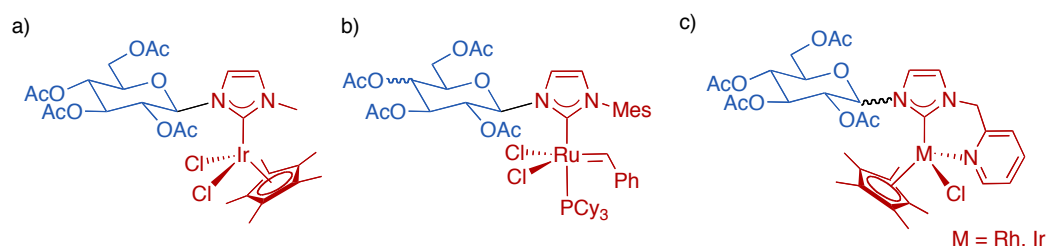
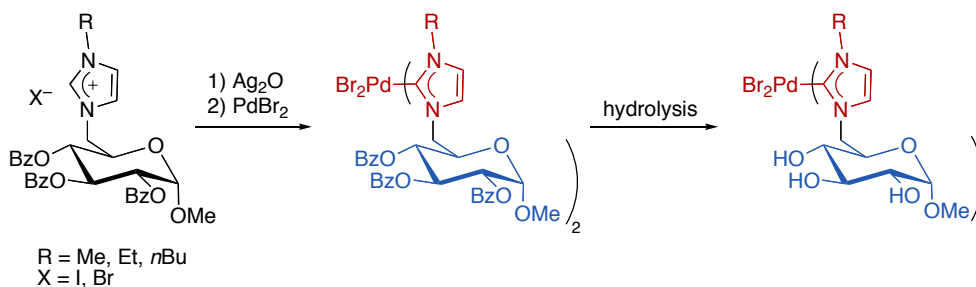


Figure 11 a) Glucose carbene iridium conjugate [48]; b) galactose and glucose ruthenium conjugate for olefin metathesis [51]; c) chiral-at-metal α - and β -glucose carbene complexes [52a].

Grubbs and co-workers have extended this approach to the synthesis of a glucopyranose- and a galactopyranose-derived imidazolyliidene ruthenium complex. Both hybrid complexes show good activity in a variety of olefin metathesis reactions (Fig. 11b) [51]. Nishioka *et al.* have recently increased the complexity and have prepared chiral-at-metal Ir(III) and Rh(III) complexes with chelating NHC ligands bearing a glucopyranosyl unit (Fig. 11c) as well as square planar NHC nickel complexes that display dynamic behaviour in solution [52]. While these early studies comprise fully protected carbohydrate NHC conjugates, Liu and Lin have succeeded in deprotecting the carbohydrate moieties to afford water soluble glucopyranoside-based biscarbene palladium(II) complexes [53]. Hydrolysis of the benzoyl protecting groups has been accomplished after metal complexation using NaOMe in MeOH followed by the

addition of aqueous HBr (Scheme 2). The resistance of the palladium–NHC unit towards harsh conditions, including strong acids and bases, demonstrates the compatibility of this synthon with physiological conditions and offers great opportunities for the application of such bioorganometallic complexes in aqueous media. As a first application, the deprotected complex is a useful catalyst precursor for Suzuki-Miyaura cross-coupling reactions in water. Product extraction allows the catalyst to be recycled easily.



Scheme 2 Synthesis of a water soluble carbohydrate-derived NHC complex [53].

Despite the evident potential of carbohydrate-derived NHC complexes in asymmetric transformations, only little is known, in contrast *e.g.* to analogous phosphine carbohydrate chemistry. The carbohydrate-functionalised ruthenium metathesis catalysts have been evaluated in asymmetric ring-opening cross-metathesis [51]. Although enantioselectivities are poor, the variety of easily available carbohydrates will likely stimulate the development of sugar-functionalised NHC complexes with enhanced stereoselectivity.

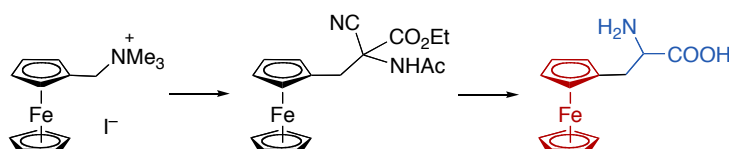
3.4 Organometallic complexes derived from amino acids and short peptides

Considering their wide abundance, homochirality and the variety of functional groups in their side chains, amino acids and short peptides are particularly attractive building blocks for the synthesis of organometallic compounds. It is thus not surprising that this area of bioorganometallic chemistry has seen substantial progress. A 1998 review on transition metal complexes with α -amino acids and peptides reflects the early interest in using these natural compounds in transition metal chemistry [54]. In most cases, the biomolecule binds to the metal centre *via* a heteroatom that is naturally located in the peptidic backbone, in the side chains of the amino acids, or available after insertion of an extra coordination site [55]. The bioorganometallic nature hence arises from M–C bonds between the metal centre and spectator ligands such as CO or π -bound ligands, in particular arenes. In contrast, this section focuses specifically on bioorganometallic complexes in which the amino acids or small peptides are carbon-linked to the metal centre. This area can be divided into three main

subgroups according to the type of carbon–metal bond: metallocenes, metal–arene (“half-sandwich”) systems, and metal–carbene complexes.

3.4.1 Metallocene bioconjugates

As in organometallic carbohydrate conjugates, ferrocene-modified amino acids and peptides have been investigated since the early stages of organometallic chemistry. Since the first synthesis of ferrocenylalanine (Scheme 3) only six years after the discovery of ferrocene [56], a variety of ferrocene conjugates with amino acids and peptides have been described. Biological as well as non-biological applications of peptide-based ferrocene complexes have been reported and the field has been competently reviewed [57]. A comprehensive overview by Metzler-Nolte covers different synthetic methods towards ferrocene bioconjugates with amino acids, proteins and other biomolecules from 1957 to 2004 [57a,b]. Neuse has collated ferrocene compounds as cancer drug models up to 2005 [57c], and Hirao has compiled work directed to supramolecular aspects and conformational control using peptide ferrocene conjugates [57d,e,58]. Two very recent reviews summarise the different applications of peptide-based ferrocene complexes in both biological and non-biological systems [12b,57f]. Due to the up-to-date and extensive reviewing of this burgeoning area of bioorganometallic chemistry, only a small selection of recent achievements is discussed here.



Scheme 3 First synthesis of ferrocenylalanine [56].

Ferrocene oligopeptide conjugates have continued to provide an attractive synthon for biosensing. Devices have been fabricated based on different amino acid sequences for the sensing of anions [59], and for the kinetic characterization of protease action [60]. A ferrocene derivative with a podant (Lys)-Leu-Val-Phe-Phe oligopeptide sequence, which constitutes the hydrophobic sequence of amyloid- β -peptides, have been demonstrated to interact with amyloid- β -peptides to form aggregates. Electrochemical monitoring of the ferrocene redox process has revealed that the strength of the interaction depends critically on the length of the peptide and its charge [61].

Zhou and coworkers have exploited the fact that the Arg-Gly-Asp peptide sequence binds selectively to integrins, which are highly expressed in tumor-induced angiogenesis. Hence this

sequence may play a key role in anticancer therapy. Combination of ferrocene with the Arg-Gly-Asp tripeptide through an aminohexanoic linker provides conjugates (Fig. 12) which show good cell uptake features and good antitumor activity ($IC_{50} = 5 \mu M$). The linker plays a critical role as the direct coupling of the tripeptide to the ferrocene lowers the biological function substantially [62].

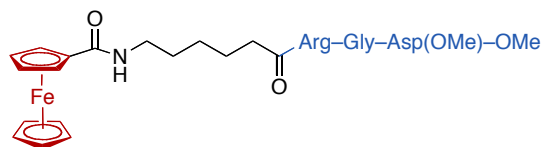


Figure 12 Ferrocene tripeptide conjugate with potent anticancer activity [62].

3.4.2 Metal–arene bioconjugates

The natural amino acids phenylalanine (Phe, F), tyrosine (Tyr, Y) and tryptophan (Trp, W) contain a benzene ring in their side chain that is available for π -bonding [63]. In 1987, Gill *et al.* have prepared the first stable $Ru^{II}(Cp)$ -arene complexes with Phe, Tyr and Trp protected at both the *N*- and *C*-terminus (Fig. 13). Ruthenium binding is induced by thermal ligand exchange from $[Ru(Cp)(MeCN)_3][PF_6]$ [64]. Of note, the unprotected heteroatoms present in the side chain of tyrosine and tryptophan do not compete with the binding of the arene to the ruthenium centre. Wolff and Sheldrick have modified the synthetic procedure to accomplish π -binding of unprotected phenylalanine to the $[Ru^{II}(cym)]$ synthon [65]. Based on these advances, π -complexation of ruthenium has been demonstrated with secretin, a linear peptide hormone constituted of 27 amino acids containing one unique Phe residue in the presence of other coordinating groups [66]. Recently it has been shown that ruthenium π -complexes of aromatic amino acids and small peptides are also accessible in water in the presence of oxygen and various potentially coordinating biomolecules including sugars and nucleotides [67]. This selectivity indicates a high orthogonality between π -bonding and donor group coordination.

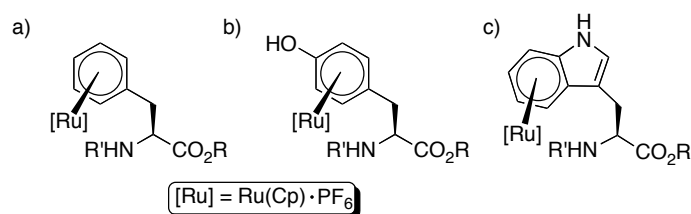
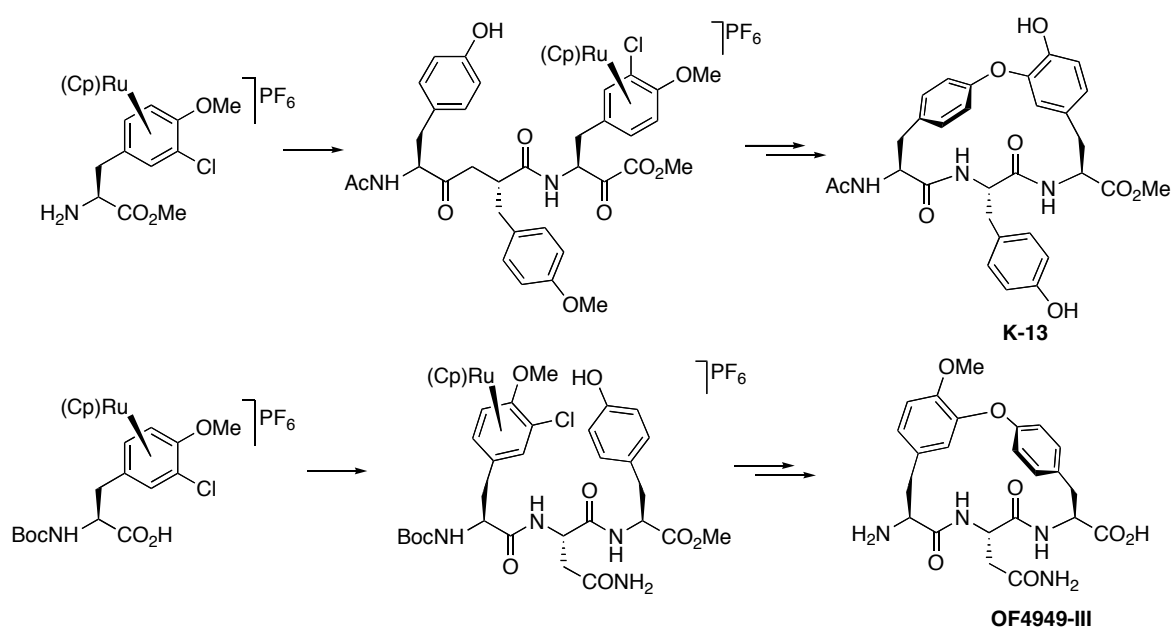


Figure 13 π -Arene ruthenium complexes with (a) phenylalanine, (b) tyrosine and (c) tryptophan [64–66].

The π -coordination of aromatic amino acids to a ruthenium(II) fragment has been applied to the synthesis of the protease inhibitors K-13 and OF4949-III and related analogues *via* S_NAr macrocyclisation. Thus, ruthenium π -arene bonding is installed at an early stage at a modified amino acid, which is subsequently coupled to afford a linear tripeptide (Scheme 4) [68]. The ruthenium centre promotes the cyclisation as a templating agent and is readily removed by photolytic cleavage. This elegant strategy highlights the high stability and versatility of ruthenium π -complexes in peptide synthesis.



Scheme 4 Synthesis of K-13 and OF4949-III *via* cyclisation of Ru–arene complexes [68].

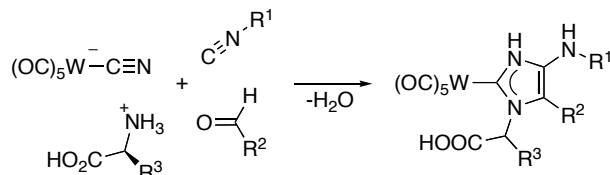
Peptide-based manganese–arene complexes are cytotoxic and display antitumor activity. Therefore, cymantrene derivatives $[\text{Cp}^R\text{Mn}(\text{CO})_3]$ with a carboxylic acid-containing substituent R on the Cp ligand have been coupled to the *N*-terminus of sC18, a cell-penetrating peptide with a GLRKRLRKFRNKIKEK sequence [69]. Modification of the linker between the Cp ring and the carboxylic acid functionality used for the amide coupling to sC18, as well as variations in the peptide sequence alter the biological activity of these bioorganometallic compounds, thus suggesting opportunities for optimisation of the antitumor activity and selectivity.

3.4.3 Metal–carbene bioconjugates

The remarkable stability of carbene complexes towards oxygen and water renders them very attractive for the synthesis of bioorganometallic compounds [70]. However, the synthesis of

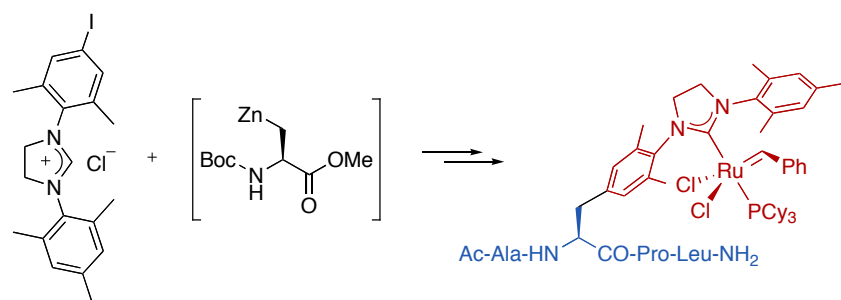
complexes with peptides bound to a metal centre *via* a carbene–metal bond has been scarcely investigated so far. Beck has developed a first synthesis of Fischer-type carbene complexes with amino acids [71]. An alkene metathesis of α,β -dehydroalanine and related amino acid derivatives with Fischer-type metal carbenes has been applied in the synthesis of Cr-, Mo- and W-pentacarbonyl complexes. Jaouen *et al.* have exploited the electrophilic characteristics of Fischer-type carbenes for the labelling of amino acid derivatives [72]. Their studies showed that primary and secondary amines in proteins react with alkoxy carbene tungsten complexes by aminolysis, which may be useful for protein crystal structure elucidation.

N-heterocyclic carbene complexes, highly popular in organometallic catalysis partly because of their high stability and activity [7], are excellently suited for the synthesis of transition metal peptide conjugates. The first N-heterocyclic carbene complexes with amino acids have been synthesised using a four-component condensation of a metal-stabilised isocyanide with an aldehyde, an organic isocyanide and an amino acid (Scheme 5) [73]. Advantageously, the resulting NHC tungsten complexes are air and water stable and may therefore find application as protein labels. However this method only allows for the synthesis of NHC complexes with specific metals and with a narrow range of carbene substituents.



Scheme 5 Synthesis of NHC complexes by four-component condensation [73].

A more general approach towards the synthesis of oligopeptidic NHC complexes relies on using imidazolium salts bearing wingtip groups that can be further modified with amino acids. Gilbertson *et al.* have used a palladium-catalysed coupling reaction between iodoaryl-substituted imidazolinium salts and an *in situ* prepared alkyl-zinc amino acid [74]. The formed imidazolinium-functionalised amino acid has been utilised in solid-phase peptide synthesis to prepare a tetrapeptide. Subsequent ruthenation with a 1st generation Grubbs catalyst affords an olefin metathesis catalyst comprised of a tetrapeptide backbone (Scheme 6).



Scheme 6 Synthesis of a Grubbs catalyst derivative containing a tetrapeptide [74].

Meldal has used unsymmetrically substituted imidazolium salts containing an α -methylene carboxylic acid, CH_2COOH , as substituent on one nitrogen and an azide or a pyridine functionality on the other nitrogen in solid-phase peptide synthesis [75]. Metallation of the resin-bound peptide-linked imidazolium salts has been performed using BEMP (2-*tert*-butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diaza-phosphorine) as a strong base and $[\text{Pd}(\text{cod})\text{Cl}_2]$ as palladium precursor. Under these conditions, the carbonyl group of the amide linker between the imidazolium and the peptide resin forms an enolate and binds to the Pd centre in a chelating manner (Fig. 14a,b). Polydentate dicarbene palladium complexes with a peptide or a pyridine linker between the two imidazolylidenes have been synthesised using a similar approach (Fig. 14c,d). Interestingly, the strong effect of carbene coordination in the complex forces a conformation of the flexible part of the peptide chain reminiscent of a β -turn (Fig. 14c), even in the absence of a proline residue in the spacer. The resin-bound NHC complexes are catalyst precursors for cross-coupling reactions and have been recycled up to eight times.

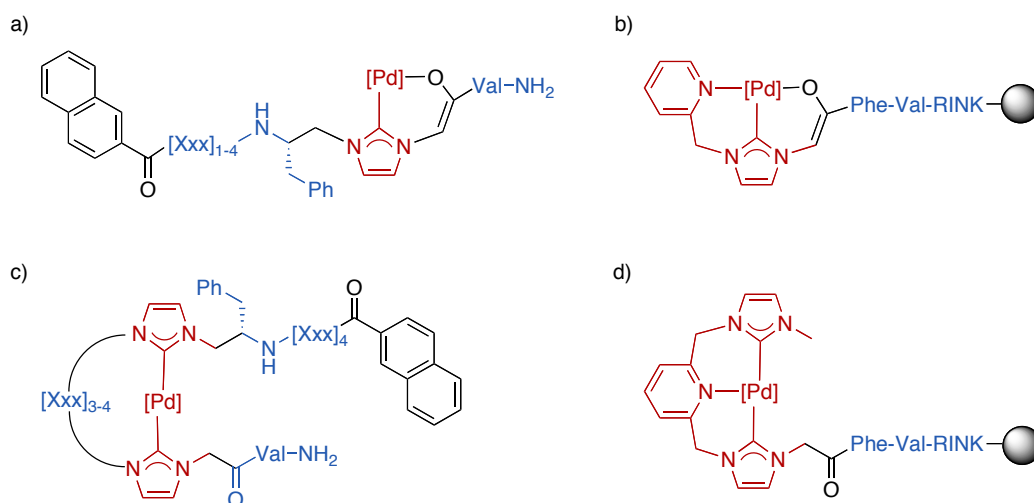


Figure 14 Peptide-base NHC palladium complexes [75].

Metzler-Nolte and co-workers have followed a similar strategy towards oligopeptide-based NHC complexes, yet using a metallated carbene rather than the imidazolium salt as synthetic building block. A pseudoenkephalin-derived ruthenium complex has thus been obtained by coupling a preformed ruthenium NHC complex with the *N*-terminus of the resin-bound tetrapeptide using solid phase peptide synthesis [76]. The NHC wingtip group contains a pentafluorophenyl benzoate as activated ester that readily undergoes transamidation to form the peptide linkage with the *N*-terminus of the resin-bound oligopeptide. After optimisation of the conditions, cleavage of the peptide from the resin has been achieved without major decomposition of the ruthenium complex (Fig. 15a). This method is not applicable to the synthesis of an analogous rhodium peptide conjugate, as the complex decomposes under the cleavage conditions. Interestingly, approaches to insert the metal centre at a later stage akin to Meldal's procedure (*vide supra*) have failed. While the imidazolium bromide with a *p*-methylbenzoic acid wingtip group has been successfully used in solid-phase peptide synthesis to form imidazolium-terminated tetrapeptides, reaction of the resin-free imidazolium peptides with silver carboxylate or silver oxide has failed to give the corresponding carbene complexes, thus preventing transmetallation with the rhodium or ruthenium precursors. In contrast, gold complexes containing a phenylalanine bound to the NHC (Fig. 15b) have been successfully synthesised from an imidazolium bromide precursor using a transmetallation procedure *via* a silver carbene intermediate [77]. The high stability of these complexes and their acceptable activity against cancer cells show great promise for further medicinal applications.

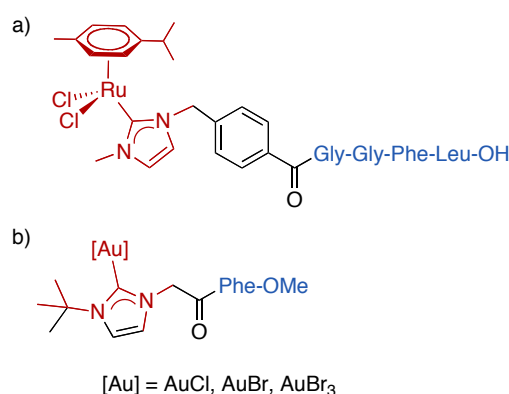
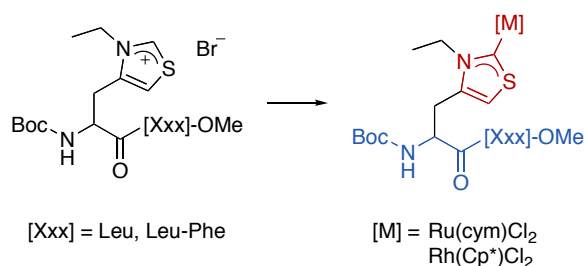


Figure 15 *N*-terminal functionalisation of peptides with NHC complexes: a) a NHC ruthenium tetrapeptide (pseudoenkephalin) conjugate [76]; b) amino acid wingtip in NHC gold complexes [77].

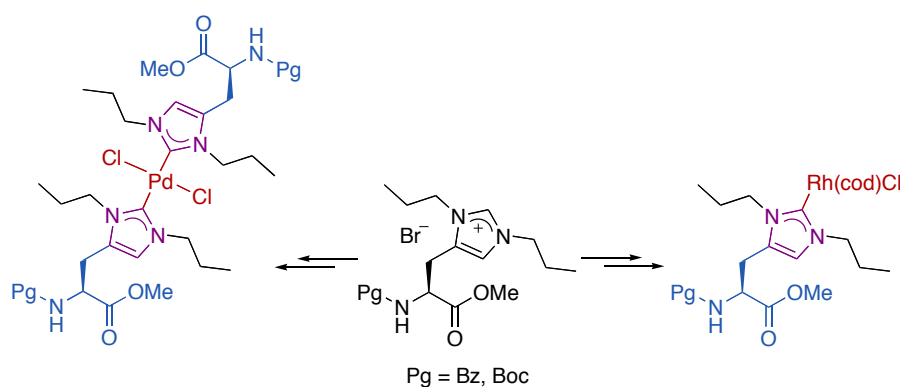
This methodology has been expanded to include the unnatural amino acid thiazolium alanine as carbene precursor [78]. This precursor is obtained by activation of the Boc-protected L-thiazolylalanine with *N*-methylmorpholine/isobutyl chloroformate and coupling to H-Leu-

OMe or H-Leu-Phe-OMe. The resulting di- and tripeptides are subsequently quaternised at the heterocyclic nitrogen to yield the oligopeptides with a thiazolium side chain (Scheme 7). Obviously, such late-stage alkylation after oligopeptide formation requires the absence of other reactive sites that are susceptible to alkylation, such as amines, alcohols or thioethers. This synthetic pathway thus restricts the range of suitable amino acids. Metallation of the thiazolium oligopeptides with rhodium(I) and ruthenium(II) is successfully accomplished by using a transmetallation procedure *via* silver carbene complexes and yields thiazolylidene complex peptide conjugates.



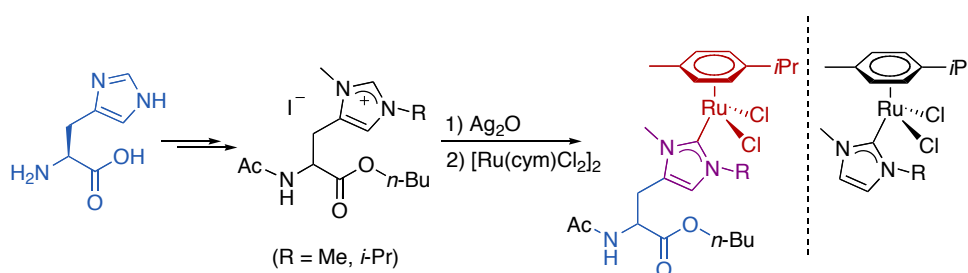
Scheme 7 Synthesis of thiazolylidene peptide complexes [78].

In pioneering work, Erker has exploited histidine as a natural starting material for the synthesis of imidazolium salts as chiral ionic liquids and ligand precursors for the synthesis of NHC carbene complexes [79]. The imidazole ring of the *C,N*-protected amino acid has been alkylated using excess alkyl halide in the presence of sodium bicarbonate, as a proton scavenger. The resulting imidazolium salts have been metallated with Ag₂O and subsequently transmetallated to afford the corresponding palladium(II) and rhodium(I) complexes as mixtures of isomers (Scheme 8).



Scheme 8 Synthesis of histidine-based NHC complexes [79].

Based on these results, we have prepared histidylidene ruthenium(II) complexes (Scheme 9), which show good activity in the catalytic transfer hydrogenation of ketones [80]. Comparison of the histidine-based NHC ruthenium complexes with imidazolylidene complexes displaying an identical first coordination sphere but lacking the amino acid backbone has shown that the remote amino acid moiety has an impact on the properties of the metal centre. Specifically, rotation about the Ru–C_{histidylidene} bond is more hindered by about 5 kJ mol⁻¹, and catalytic transfer hydrogenation is slower in the presence of an amino acid substituent.

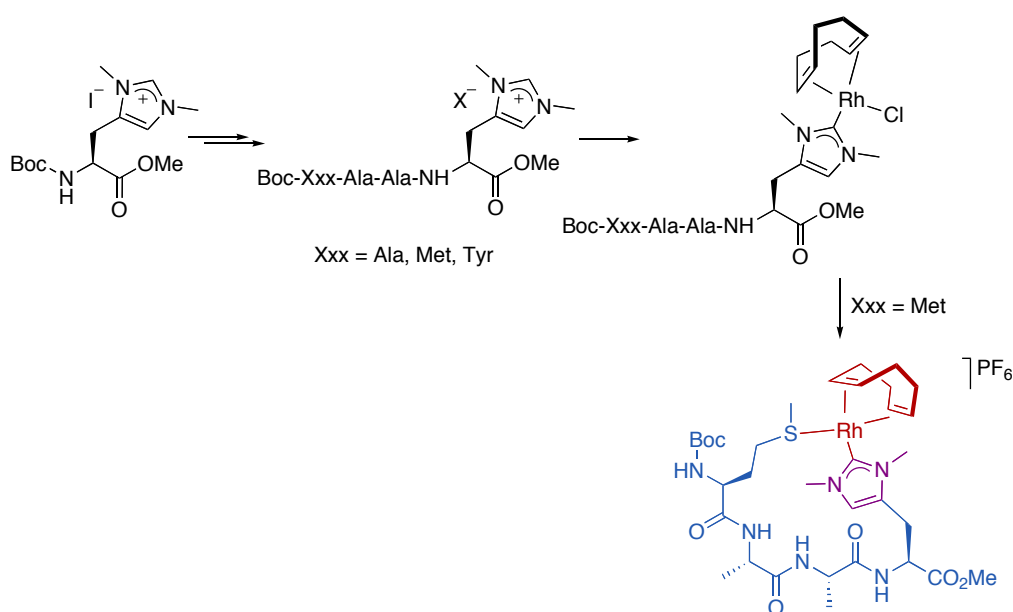


Scheme 9 Synthesis of histidylidene ruthenium complexes for transfer hydrogenation catalysis [80].

Depending on the reaction conditions, the strong basicity of Ag₂O induces proton exchange at the α -position of histidine, resulting in partial or full racemisation. The stereospecificity of the silver carbene formation has been probed by transmetallation with [Rh(cod)Cl]₂ and subsequent ligand exchange of the chloride by (*S*)-Ph-binepine as a chiral reporter. Diastereomeric mixtures are readily distinguished by ³¹P NMR spectroscopy of the corresponding carbonyl complexes. Accordingly, prolonged reaction time and elevated temperatures for the formation of the silver carbene complex promote racemisation, while short treatment of the histidinium salt with fresh Ag₂O in CH₂Cl₂ prevents racemisation and entails stereospecific (trans)metallation [81].

Biochemical modification allows the histidinium salt to be anchored to short peptides. Metallation of the histidinium-containing tri- and tetrapeptides under optimised stereospecific conditions has been successfully demonstrated and affords histidylidene iridium(III) and rhodium(I) complexes (Scheme 10). Incorporation of methionine at the *i*+3 position provides a potentially chelating site. Coordination of the *S*_{Met} donor site is induced by halide abstraction from the rhodium centre and yields a tetrapeptide-based macrocyclic NHC rhodium complex, which is catalytically competent in the hydrosilylation of ketones [82]. Much higher turnover frequencies at 50% conversion (TOF₅₀ $\approx$ 1200 h⁻¹) are observed when the histidylidene ligand is *C,S*-bidentate bound to the rhodium centre as compared to the

monodentate histidylidene rhodium complex comprising a dangling tetrapeptide sequence ($\text{TOF}_{50} \approx 60 \text{ h}^{-1}$). Chelation is ubiquitous in metalloenzymes, typically featuring a di- or triade of amino acid side chains bound to the metal centre. The catalytic benefit noted with these artificial systems provide attractive opportunities for the use of histidine-containing peptides as NHC ligands in catalysis [82].



Scheme 10 Synthesis of oligopeptide-embedded histidylidene rhodium complexes [82].

3.4.4 Miscellaneous *M*–*C* bioconjugates

Van Koten and co-workers have combined NCN pincer platinum complexes with α -amino acids to generate organometallic bioconjugates (Fig. 16a). Valine-functionalisation has been achieved by a reductive amination of the NCN-Pt unit at the formaldehyde substituent on the pincer ligand. The formed hybrid system has been suggested as a potential marker due to the unique ^{195}Pt NMR signal, and as (bio)sensor since the Pt–NCN unit provides a diagnostic colorimetric and spectroscopic response to the presence of SO_2 gas or iodine [83]. For example, a 1000 ppm upfield shift is observed upon reversible SO_2 adduct formation. Related pincer palladium(II) complexes have been covalently attached to either the *N*- or the *C*-terminus of valine and to the *N*-terminus of a Phe–Val dipeptide (Fig. 16b,c). These palladium peptide conjugates are moderately active in the aldol condensation of methyl isocyanate and benzaldehyde and provide the isoxazoline as a mixture of *cis* and *trans* isomers [84].

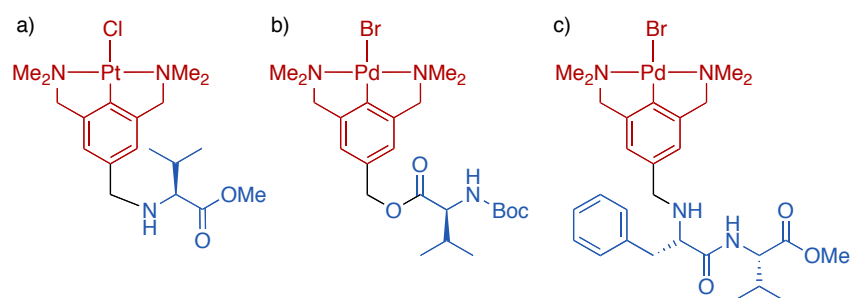


Figure 16 Bioconjugates from combining pincer complexes with α -amino acids [83,84].

Artificial mono- and dipeptides functionalised with alkyne groups at the *N*- and *C*-terminus coordinate to tungsten to form metallocyclic peptides [85]. Alkynes have also been introduced in amino acid side chains, for example in β -alkynylalanine [86]. Incorporation of this synthetic amino acid in an oligopeptide sequence and subsequent metallation with $\text{Co}_2(\text{CO})_8$ yields a dicobalt-hexacarbonyl alkyne peptide bioconjugate (Fig. 17). Further functionalisation of the *N*-terminus with ruthenocene affords a heterotrimetallic $[\text{RuCo}_2]$ peptide with all metals bound exclusively to carbons. This organometallic peptide system exhibits moderate cytotoxicity against specific tumour cell lines [87].

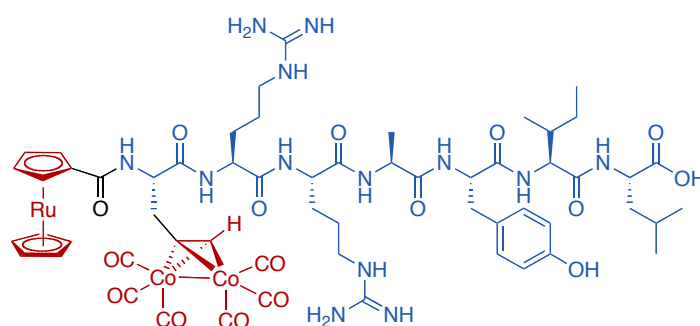
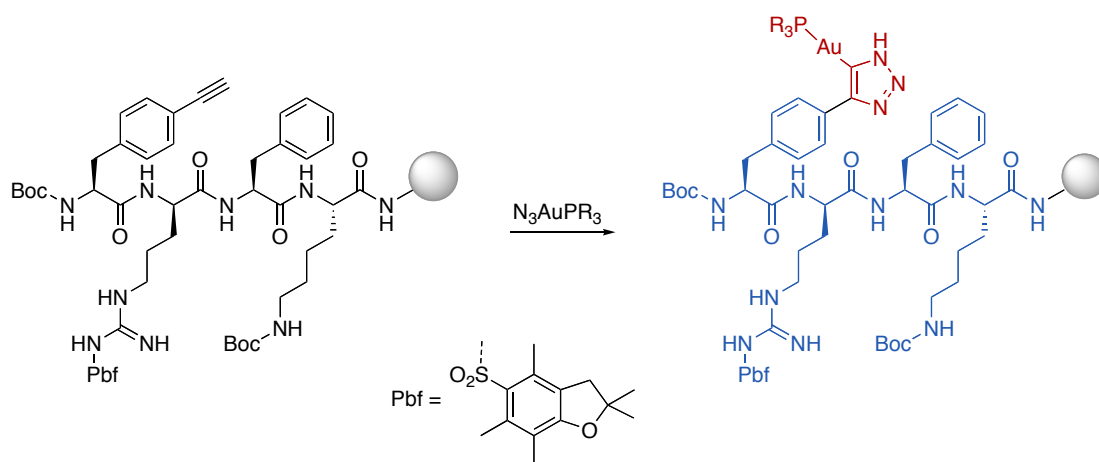


Figure 17 Ruthenocene dicobalt-hexacarbonyl alkyne peptide bioconjugate [87].

Building on these reactivity patterns, *p*-alkyne-substituted phenylalanine has been used in solid-phase peptide synthesis. Reaction with a (phosphine)gold azide complex induces a [2+3] cycloaddition and affords a triazolyl gold complex covalently attached to the peptide scaffold (Scheme 11) [88]. Dissociation of the organogold peptide conjugate from the solid support yields a gold oligopeptide conjugate with activity against some cisplatin-resistant breast cancer cell lines.



Scheme 11 Synthesis of a tetrapeptide triazolyl (phosphine)gold(I) complex with antitumor activity [88].

4 Conclusions

The rapid growth of bioorganometallic chemistry over the last decade demonstrates the great opportunities arising from using biomolecules as ligands for organometallic compounds, and *vice versa*, from incorporating organometallic entities as functional sites within biomolecules. Bioorganometallic systems have found applications in various areas such as bioanalysis, medicinal, supramolecular, and materials chemistry, and catalysis. The increasing number of organometallic complexes with a robust M–C bond in water and over a broad pH range combined with the availability of efficient and versatile coupling methodologies will certainly further stimulate advances in bioorganometallic chemistry. It seems particularly attractive to harness the high (asymmetric) selectivity of biological scaffolds for promoting the development of transition metal conjugates in catalysis, diagnostics, and other medicinal applications.

An inherent challenge associated with metal carbene bioconjugates consists of the hugely different scales of organometallic entities and biomolecules, especially when macromolecular scaffolds such as enzymes or DNA is involved. These challenges pertain both to synthesis (stoichiometry, purification) and analysis, and area will undoubtedly profit from the on-going progress in refining microscopic techniques. Site-specific and stoichiometrically defined functionalisation will provide attractive opportunities for a variety of biologically relevant areas, including for example the monitoring of protein folding processes or the uncovering of DNA-drug interactions. Due to the more covalent character of a metal-carbon bond as opposed to a metal-heteroatom bond, organometallic species are kinetically typically more robust and

may thus provide significant advantages for probing of function, the targeted delivery of pharmacologically active substances, and for repetitive sensing.

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