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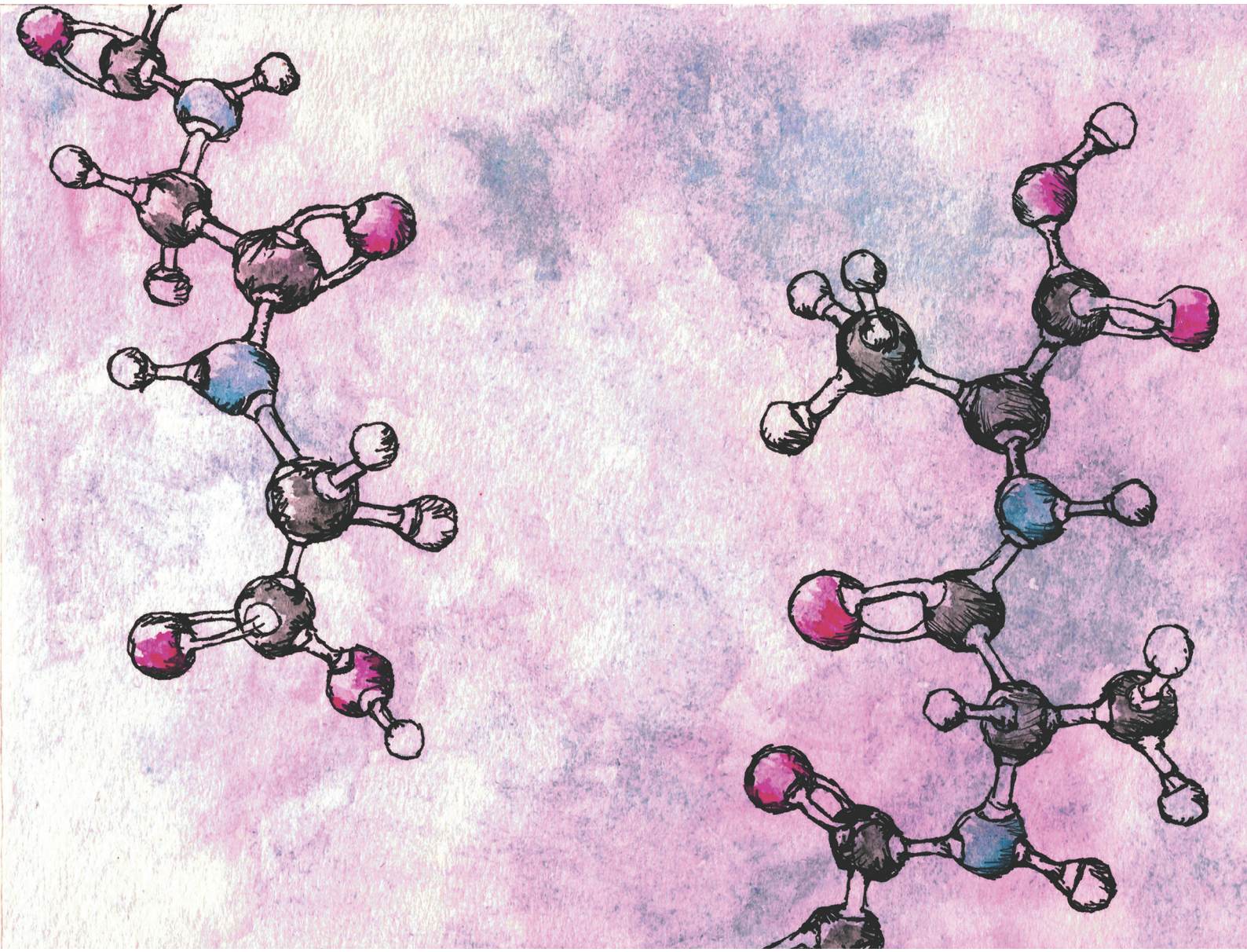

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REVIEW ARTICLE
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REVIEW

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Synthesis of metal-binding amino acids

Katherine E. V. Deck * and William D. G. Brittain *

The ability for amino acid residues to bind metals underpins the functions of metalloproteins to conduct a plethora of critical processes in living organisms as well as unnatural applications in the fields of catalysis, sensing and medicinal chemistry. The capability to access metal-binding peptides heavily relies on the ability to generate appropriate building blocks. This review outlines recently developed strategies for the synthesis of metal binding non-proteinogenic amino acids. The chemistries to access, as well as to incorporate these amino acids into peptides is presented herein.

1. Introduction

There are many examples of naturally occurring peptides and proteins which are capable of binding metal ions. In fact, metalloproteins carry out many important roles within living organisms from oxygen transport to tumor suppression, which depend on the proteins haemoglobin and p53 respectively Nature utilizes its collection of proteinogenic amino acids to facilitate metal binding with residues such as histidine, methionine and cysteine commonly employed. These naturally occurring residues have been exploited in de-novo protein design and synthesis to allow access to a range of metal binding peptides.[1,2a,b] This has been a highly fruitful area with systems such as peptide coiled-coils showing high affinities for metal binding in combination with the ability to accommodate metals that are not commonly found in biological environments (*e.g.* lanthanides/actinides).[3] De-novo peptide design allows for applications that natural proteins are not suitable for such as catalysis, metallodrugs or contrast agents.[4] Whilst these proteinogenic residues can bind metals they are limited in their scope and flexibility. In the area of synthetic chemistry many motifs have been developed which are capable of binding metal ions with high affinity. Many of these motifs have then been applied successfully in areas such as transition metal catalysis, chemical sensing and medicinal chemistry. In particular these advances have allowed for insights to be gained into structural biology and biosynthetic pathway elucidation revealing the critical roles that metalloproteins play with organisms. The motifs and ligands do not have to be confined to the naturally occurring functional groups found within genetically encoded amino acids which means they can have increased function and flexibility that proteinogenic amino acids are incapable of. Therefore, a growing area of interest is the incorporation of novel metal-binding residues and motifs into peptides and peptidomimetics.

Non-canonical amino acid building blocks comprise a vital part of the repertoire of methodology for engineering synthetic metallopeptides and peptidomimetics. The demand for readily accessible building blocks with simple installation has grown over the past decade as the interest in metal-binding peptide materials for wide-ranging applications continues to increase.

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Katherine E. V. Deck (Right) and William D. G. Brittain (Left)

Katherine obtained a MSci degree in Natural Sciences from Durham University in 2023, specialising in chemistry and biology with a final year project in the O'Donoghue group focusing on stable radical bioconjugation. As an undergraduate she carried out two summer research projects under the supervision of Dr William Brittain, for which she was awarded the prize of Student Employee of the Year 2023. She has since joined the Brittain Group as a PhD student as part of MoSMed CDT in collaboration with Dr Patricia Muller (Department of Biosciences) where she is working on designing novel anticancer peptides.

Will completed his PhD at the University of Birmingham working with Prof. John Fossey and Prof. Ben Buckley in 2017. He then moved to Durham University to undertake postdoctoral studies with Prof. Steven Cobb. In 2021 he began a Leverhulme Early Career Fellowship studying metal binding peptides before being appointed as an Assistant Professor of Organic Chemistry in 2024. Later in 2024 he was promoted to Associate Professor at Durham University. His group specialises in organofluorine chemistry and peptide synthesis.

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This review will discuss the development of methodology for the synthesis of metal-binding amino acids, and examples of how these building blocks have been utilized both in peptide synthesis and in wider applications. Amino acid examples will be categorized either by the identity of the metal binding atoms or metal-binding functional group.

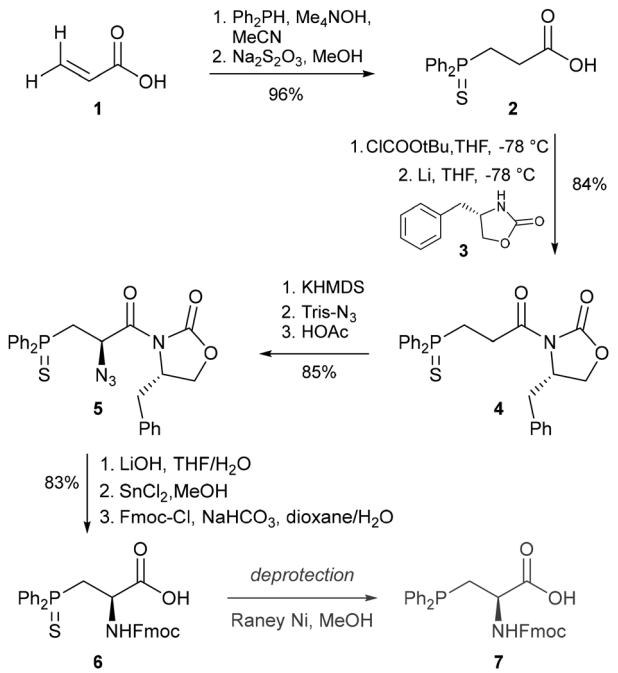
2. Phosphorus-containing amino acids

2.1. β-Phosphino amino acids

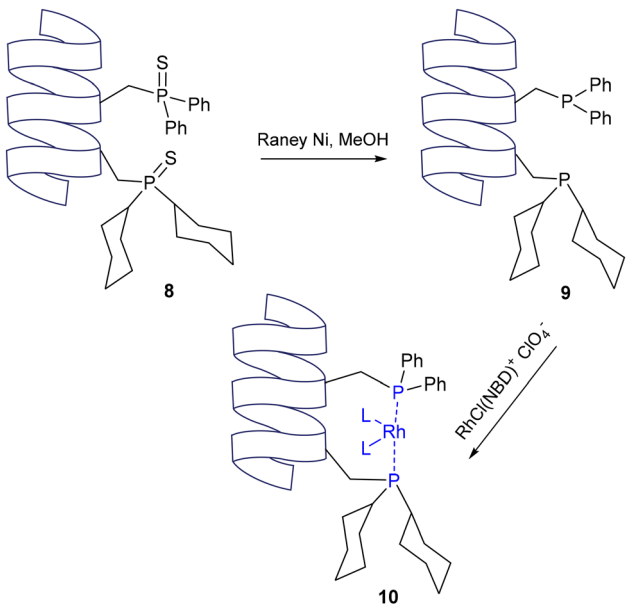
Owing to their electronic and steric tunability, phosphine ligands are highly versatile within transition metal catalysis and applicable to a wide range of organic transformations. These range from C–C bond forming reactions, *e.g.* Suzuki and Heck couplings, to Rh(I)-catalysed olefin hydrogenation.[5a,b] Functionalisation of amino acids with phosphine moieties was pioneered by Gilbertson and co-workers in 1994, who first reported a synthetic route to diphenylphosphinoserine (Pps) sulfide **5** using Evan's chiral oxazolidinone chemistry (Scheme 1).[6] Treatment of acrylic acid **1** with diphenylphosphine under basic conditions afforded carboxylic acid **2** in 96% yield, from which oxazolidinone **4** was formed through coupling to **3**. The diastereomeric azide **5**, formed by reaction of triszyl azide with the enolate of **4**, was separated chromatographically and treated with lithium hydroxide to cleave the chiral auxiliary. Reduction to the amine with tin(II) chloride followed by installation of the Fmoc protecting group gave the desired amino acid **7** suitable for direct incorporation into a peptide by solid phase peptide synthesis (SPPS).

The same was applied soon after to synthesize (dicyclohexylphosphino)serine (Cps) and its sulfide precursor, which was incorporated into a 12mer peptide sequence along with the previously reported Pps sulfide.[7] This peptide (**8**) was then treated with RANEY® nickel and methanol to reduce the sulfide-bearing P(V) centre to the corresponding P(III) phosphine, enabling subsequent metallation by addition of a Rh(I) salt. By placing these residues at the *i* and *i* + 4 positions of the α-helical peptide, the phosphine moieties were brought into the correct orientation to allow for metal coordination *via* the phosphorus atoms (Scheme 2).

To structurally diversify the peptides obtained from incorporating these amino acids, Gilbertson and co-workers sought to devise a synthetic route to Fmoc-protected phosphanyl-substituted proline **16**, with the aim of inducing a β-turn structure upon its incorporation into a peptide tetramer.[8] The original strategy started with 4-hydroxyproline **11**, from which the *N*-protected compound **12** was formed *via* mesylation with methanesulfonyl chloride (Scheme 3A). Additionally, protection of the carboxylic acid moiety was required to avoid reaction with the phosphide nucleophile – initial attempts using a variety of ester protecting groups were unsuccessful, therefore it was decided to convert the acid substrate into the corresponding TBDMS-protected alcohol **13** to enable selective attack of the phosphide at the 4-hydroxy position. Subsequent removal of the *N*- and *O*-protecting groups gave **14** which was readily converted to either the Fmoc- or Boc-protected amino alcohol. Although ultimately successful in generating both protected proline derivatives, this approach necessitated a challen-



Scheme 1 First reported synthesis of an amino acid functionalised with a phosphine moiety – Gilbertson and co-workers.[6]



Scheme 2 Formation of a Rh(I) complex within an alpha helical peptide containing phosphine-functionalised residues at the *I* and *I* + 4 positions – Gilbertson and co-workers.[7]

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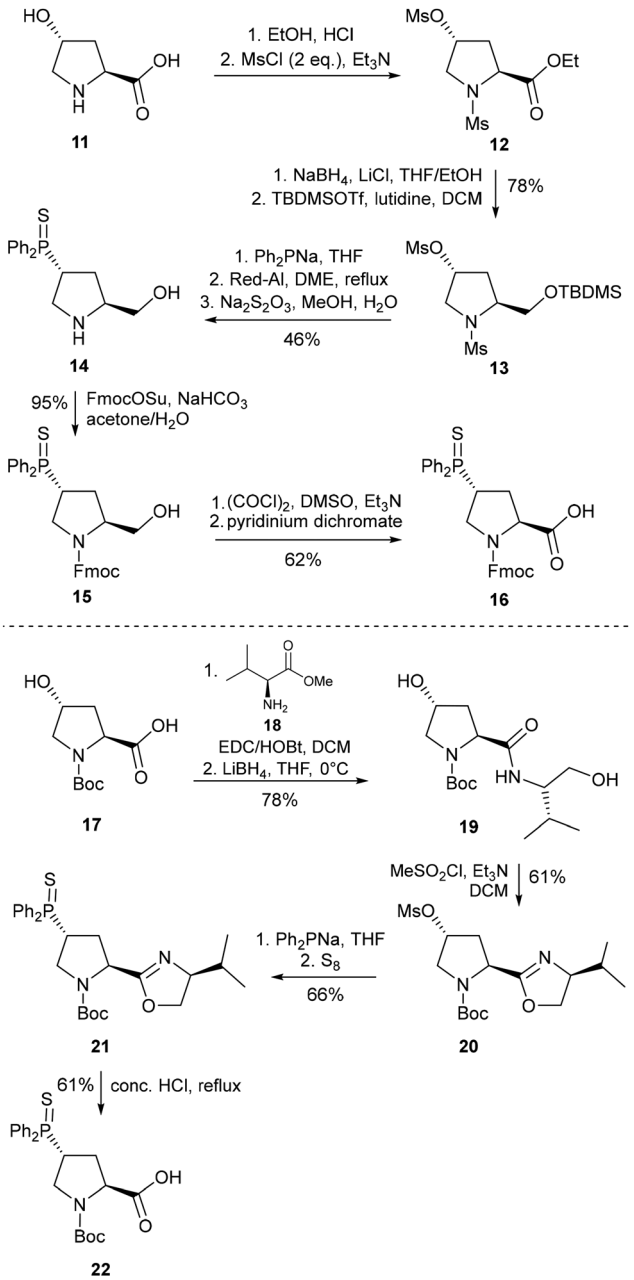
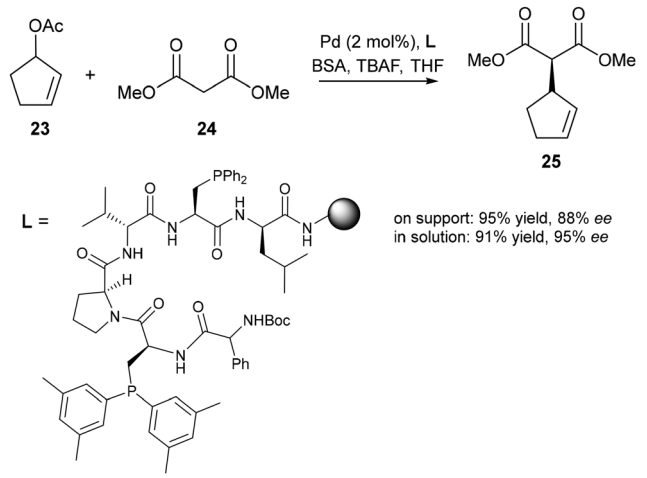


Scheme 3 Synthesis of phosphino-proline derivatives *via* (A) nucleophilic displacement and (B) chiral oxazolidone – Gilbertson and co-workers.[8,9]

ging selective oxidation sequence to reform the carboxylic acid while leaving the phosphine sulphide group intact. A more streamlined approach was later developed by the same group that utilised an oxazoline acid protecting group to allow for nucleophilic substitution of the mesyl-alcohol **20** with sodium diphenylphosphide, followed by acidic hydrolysis to reform the carboxylic acid **22** as desired (Scheme 3B).[9]

Following on from these examples of peptidic phosphine ligands with rhodium-coordinating capabilities, a 63-member library of diphosphine peptides was produced using combinations of Pps and Cps residues in varying orientations, with α-aminoisobutyric acid (Aib) residues included to enforce a helical secondary structure. Each of these peptides were complexed to rhodium and screened for their catalytic activity in the asymmetric hydrogenation of methyl 2-acetamidoacrylate.[10] Although some degree of selectivity was observed, and later improved upon in a subsequent 2nd generation library,[11] the consistently low to moderate enantiomeric excesses (up to 36% ee) led the authors to change their focus towards peptides featuring a β-turn secondary structural element.[12] This proved fruitful, with peptides containing the well-known β-turn forming motif –Pro-D-Yyy– (where Yyy is a D-amino acid)[13a,b] flanked by diphenylphosphinoserine **7** showing up to 95% ee in the Pd-catalysed addition of dimethylmalonate **24** to 3-acetoxycyclopentene **23** (Scheme 4).[14]

An alternative strategy towards β-phosphino amino acids was reported in 1998 by Burgess and co-workers, enabling access to the D-enantiomer of Pps(sulfide) starting from L-serine (Scheme 5).[15] Using a previously reported procedure to form Boc-protected oxazolidine **27**,[16] tosylation to give **28** enabled installation of the diphenylphosphine group through nucleophilic substitution with the corresponding phosphide. Subsequent sulphuration of the phosphorus centre gave **29**, of which the oxazolidine ring could be cleaved by treatment with aqueous acid. Despite the need to reintroduce the Boc protecting group, **30** was obtained in high yield, from which **31** was formed in 99% ee by oxidation of the alcohol using pyridinium dichromate. A similar approach was later attempted by Stelzer and co-workers with the intention of developing a strategy applicable to a larger scale (Scheme 6).[17] Use of a Ph_2PH/K_2CO_3 heterogeneous system under solid–liquid phase transfer conditions enabled *in situ* generation of the anionic phosphide nucleophile, which reacted readily with L-iodoalanine **34**, formed through treatment of *O*-tosylated *N*-Boc-L-serine **33** with sodium iodide. Although the corresponding phosphines



Scheme 4 Palladium-catalysed allylic alkylation of dimethylmalonate with cyclic substrate 3-acetoxycyclopentene using the phosphine-containing β-turn peptide Boc–D-Phg–Xps–Pro–D-Val–Pps–D-Leu–OMe – Gilbertson and co-workers.[14]

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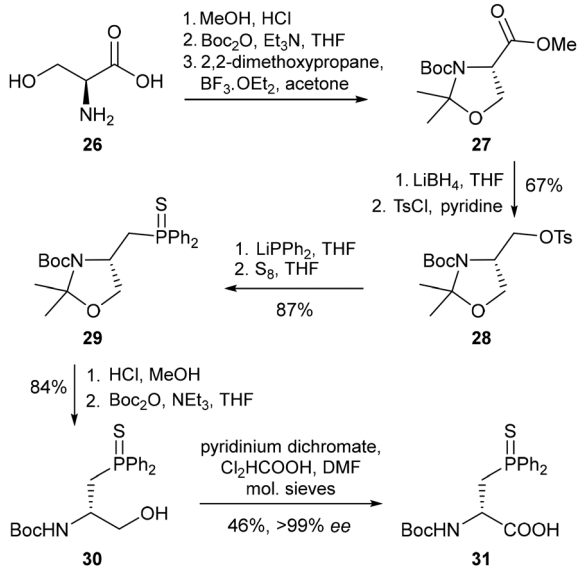
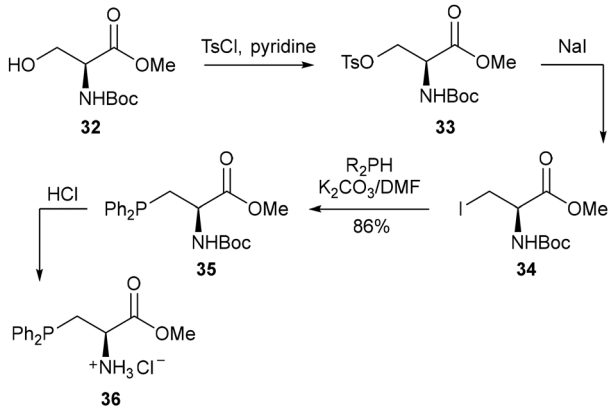


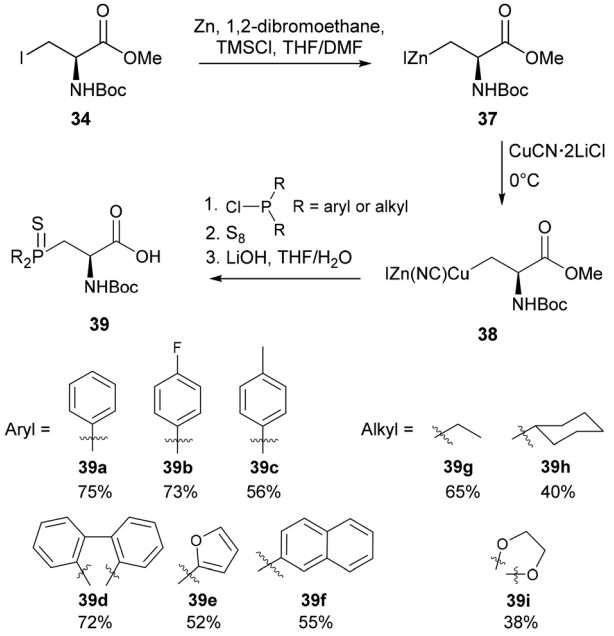
Scheme 5 Synthesis of the D-enantiomer of the phosphine-containing amino acid Pps – Burgess and co-workers.[15]



Scheme 6 Synthesis of Pps using a heterogenous catalysis approach – Stelzer and co-workers.[17]

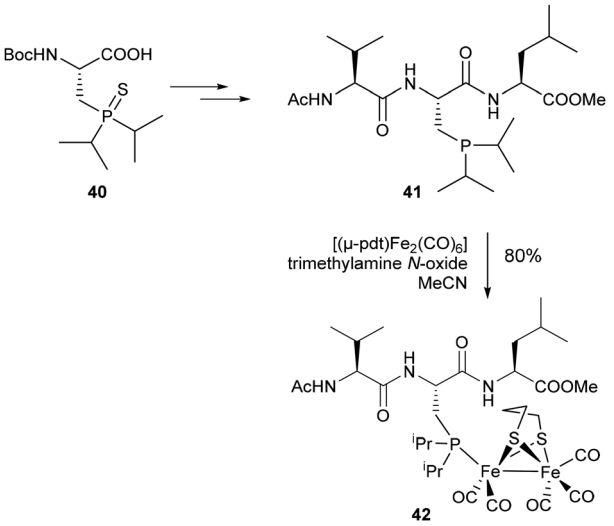
were obtained in high yield, racemisation at the α-carbon was a major issue.

Based on precedents set for the use of iodozinc reagents in the synthesis both of phosphines and unnatural amino acids,[18a,b] Gilbertson and co-workers demonstrated that a range of phosphinoserine derivatives could be efficiently synthesized by coupling nucleophilic zinc/copper reagent **38** to an electrophilic chlorophosphine (Scheme 7).[19] Using Knochel's procedure for the preparation of functionalised copper reagents,[20] iodozinc **37** is readily accessible from treatment of commercially available *N*-Boc iodoalanine **34** with activated zinc, which can subsequently be converted into **38** following stoichiometric addition of the copper salt. Treatment of this reactive intermediate with various aryl and alkyl chlorophosphine reagents afforded a new library of phosphine-containing amino acids **39a-I** in yields ranging between 40% and 75%.



Scheme 7 Synthesis of aryl and alkyl phosphinoserine derivatives *via* zinc/copper mediated P–C coupling – Gilbertson and co-workers.[19]

This method would later be implemented in 2015 by Roy and co-workers in the design of diiron analogues of [FeFe]-hydrogenases, who demonstrated the incorporation of the diphenyl-, diethyl- or previously unreported diisopropylphosphine-functionalised amino acid **40** into a model hydrophobic tripeptide sequence (**41**) using solution-phase peptide synthesis. Metalation with (μ-pdt)$Fe_2(CO)_6$ afforded the desired phosphine-substituted diiron complex **42**, which was subsequently found to exhibit electrocatalytic activity in the presence of acetic acid in mixed aqueous–organic solutions (Scheme 8).[21]



Scheme 8 Incorporation of a diiron complex into a tripeptide *via* a phosphine moiety for the formation of a biomimetic model of a [FeFe]–hydrogenase – Roy and co-workers.[21]

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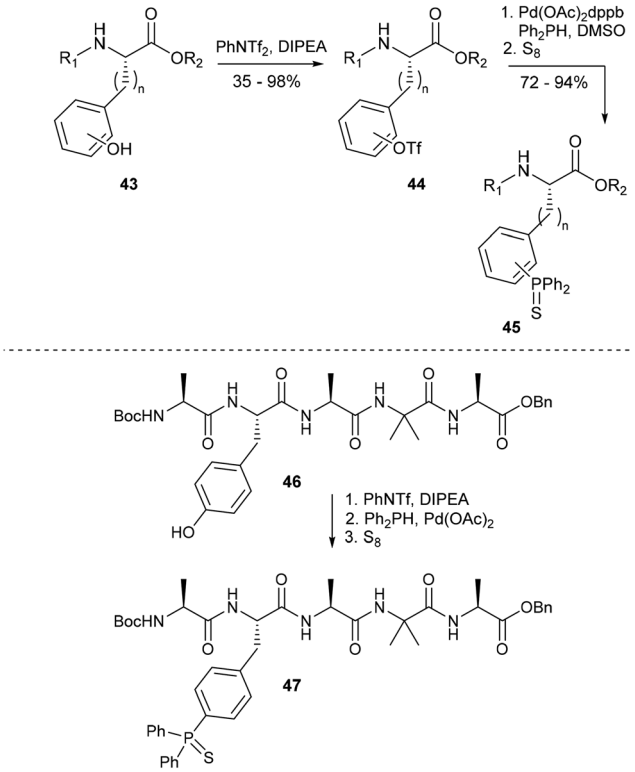
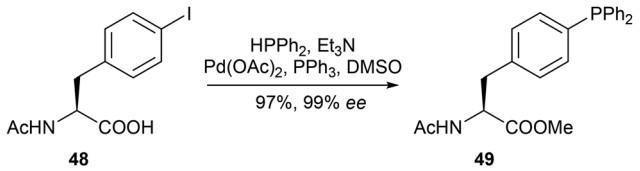
2.2. β-Phosphino derivatives of aromatic amino acids

Following their successful synthesis of serine derivatives, Gilbertson and coworkers sought to expand the selection of phosphine-bearing building blocks to include aromatic amino acids. Taking inspiration from the well-established Stille coupling of aryl halides with diphenylphosphines,[22] combined with the existing precedent of palladium-catalysed couplings with aryl triflates,[23] a method was developed for the catalytic conversion of the phenolic hydroxyl group of tyrosine **43** to the arylphosphine ligand **45** *via* the corresponding aryl triflate **44** (Scheme 9).[24] Additionally, this method was applied directly to a pentapeptide (**46**) bearing a tyrosine residue, demonstrating a convenient alternative to the individual preparation and installation of phosphine amino acids into peptides. Kraatz reported a similar method utilising palladium catalysis to couple iodophenylalanine **48** to diphenylphosphine, giving rise to *N*-acetyl protected diphenylphosphanyl derivatives of D- and L-phenylalanine (**49**) without racemisation (Scheme 10).[25]

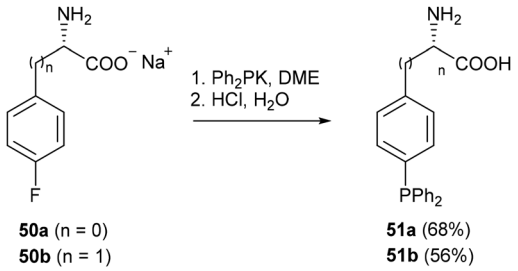
Contrastingly, phosphinophenylglycine and -alanine derivatives **51a–b** were synthesized by Stelzer and co-workers *via* nucleophilic aromatic substitution starting from the sodium salts of 4-fluoro-α-phenylglycine (n = 0) and -alanine (n = 1).[26] Treatment of salts **50a–b** with potassium diphenylphosphide leads to attack of the phosphide anion at the 4-position with loss of fluoride to give *para*-substituted phosphinophenylamino acids **51a–b** respectively (Scheme 11). This methodology was later extended to include the analogous *ortho*-substituted derivatives, synthesized from the corresponding 2-fluoro-α-phenylglycine and alanine salts.[27]



Scheme 9 Transformation of (A) *N*-protected tyrosine esters and (B) a tyrosine residue in the peptide Boc–Ala–Tyr–Ala–Aib–Ala–OBn, into aryl phosphine ligands *via* the corresponding triflate – Gilbertson and co-workers.[24]



Scheme 10 Palladium-catalysed synthesis of phosphine-containing aromatic amino acids – Kraatz and co-workers.[25]



Scheme 11 Synthesis of diphenylphosphine derivatives of phenylglycine and -alanine derivatives *via* SnAr chemistry – Stelzer and coworkers.[26]

2.3. Other phosphorus-containing amino acids

While the phosphine moiety makes up a considerable portion of phosphorus-based ligand chemical space, several other ligand classes have appeared in the literature for incorporation into peptides for various metal-binding applications. The following section includes discussion of amino acids functionalised with phosphole, phosphinite and phosphate moieties – for a recent in depth review on the synthesis of other phosphorus-containing amino acids see the provided ref. 28.

2.4. Phosphole amino acids

Like the phosphine group, phospholes comprise an important class of phosphorus(III) donor ligand broadly applicable to a variety of metal-catalysed transformations.[29] The use of these P-heterocyclic ligands has been widely reported both in standard and asymmetric reactions, from their initial emergence in rhodium-catalysed hydrogenation[30] and hydroformylation processes,[31] to more recent examples such as catalytically active phosphole-containing porphyrin-derived platforms[32] and phosphole-embedded helicenes for use in enantioselective gold catalysis.[33] Aside from catalysis, phosphole metal complexes have been used in biomedical research, owing to their well-documented activity as disulphide reductase inhibitors.[34] Bioconjugation is a well-established strategy for the development of metallopharmaceuticals with suitable pharmacological characteristics. A notable example of this is the anti-arthritic drug Auranofin (**52**), approved by the FDA in 1985,

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which is comprised of a thiosugar and phosphine ligand coordinated to a Au(I) centre (Fig. 1).[35] More recently, modification of a phosphole Au(I) complex with a thiosugar (**53**) was demonstrated to increase bioavailability whilst retaining antiproliferative potency.[36]

The first reported phosphole-containing amino acid **58** was synthesized in 2007 by Le Floch and co-workers, starting from *N*-Boc serine **54** (Scheme 12).[37] The carboxylic acid was converted to the corresponding methyl ester using methyl iodide, followed by treatment with triphenylphosphine and iodine in the presence of imidazole to form the iodoalanine methyl ester (**34**). The phosphole species (**56**) was then generated by reacting **34** with the lithium salt of 3,4-dimethylphospholide (**55**). As with the phosphine-containing amino acids described in section, the phosphorus(III) centre in **56** is highly prone to oxidation, therefore protection of the lone pair was carried out with elemental sulphur to form the sulfide derivative **57**. This sulphide-protected phosphole moiety was found to be highly stable throughout manipulation of the amino nitrogen protecting groups, ultimately enabling formation of the desired Fmoc-protected amino acid **58** for potential applications in peptide synthesis.

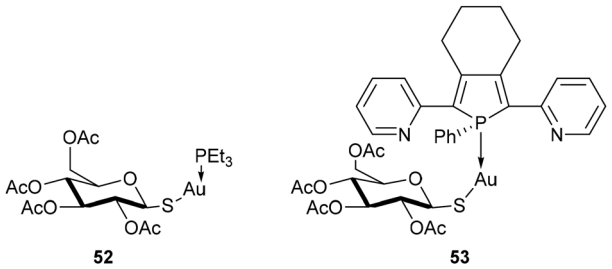
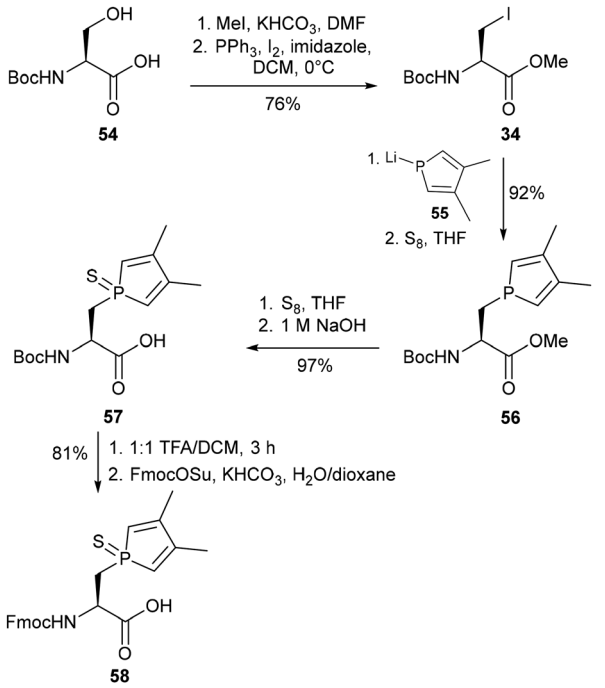
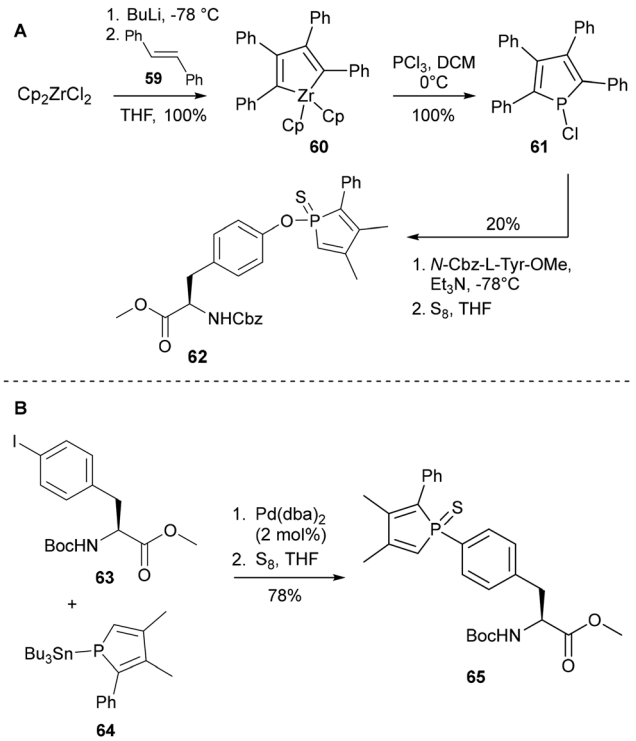


Fig. 1 Auranofin **52** and phosphole analogue **53** – Bagrel and co-workers.[36]



Scheme 12 Synthesis of a phosphole-containing amino acid **58** – Le Floch and co-workers.[37]

In 2010, the same group reported two new synthetic strategies towards the incorporation of the phosphole moiety into aromatic amino acid sidechains.[38] Functionalisation of the tyrosine hydroxyl group was envisaged *via* a nucleophilic substitution approach – a method frequently seen for the installation of an alkoxy group to a phosphorus centre,[39a,b] although not previously applied to the phosphole functionality specifically. The key component of the synthesis, chlorophosphole **61**, was accessed *via* metallacycle transfer reaction of the corresponding organozirconium **60**, prepared from Cp_2ZrCl_2 and *n*-butyllithium as reported by Negishi in 1986.[40] Reaction of chlorophosphole **61** with readily available Cbz-protected tyrosine methyl ester at −78 °C in the presence of base led to formation of the desired amino acid **62**, albeit in a relatively low yield (Scheme 13A). The second strategy utilised a Pd-catalysed Stille cross-coupling between the *N*-protected amino acid methyl ester **63** and substituted stannylphosphole reagent **64**. While no reaction was observed for attempted couplings with the *N*-Cbz tyrosine triflate methyl ester, even in the presence of catalytic amounts of Cu(I) halide salts, full conversion was seen when *N*-Boc 4-iodophenylalanine methyl ester **63** was instead used (Scheme 13B). The phenylalanine phospholyl-



Scheme 13 Functionalisation of aromatic amino acids with a phosphole moiety *via* (A) nucleophilic substitution and (B) Stille cross-coupling – Le Floch and co-workers.[38]

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derivative **65** was ultimately obtained following protection of the phosphorus lone pair with a sulphide group.

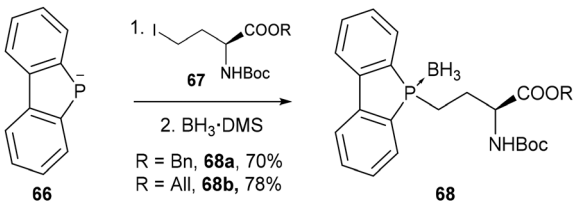
Although the sulphide group confers adequate stability to the otherwise free P(III) centre of the amino acid, the occurrence of racemisation during manipulation of this protecting group cannot be fully ruled out. Convincing data surrounding the enantiomeric purity of these amino acids has remained sparse, and the reported deprotection procedure *via* reductive desulphurisation with RANEY® nickel has been previously reported to cause racemization at the α-carbon of phosphine-based amino acids, ultimately leading to the generation of diastereomeric peptides.[21] More recently, Cavelier and co-workers detailed a modified approach to the preparation of phospholyl amino acids and peptides, in which the limitations of previous methodology were addressed.[41] Specifically, substitution of SPPS-compatible *N*-protected iodo amino esters **67** with deprotonated phospholide **66** followed by addition of borane dimethyl sulphide led to the formation of *N*-protected phospholyl(borane) amino esters **68** in up to 99% ee, as determined by chiral HPLC (Scheme 14). The applicability to peptide synthesis was effectively demonstrated through the formation of dibenzophospholyl(borane) dipeptide derivatives through *N*- and *C*-amide coupling with an alanine residue. The use of borane as a complexing agent enabled the racemization-free transformation of the phospholyl amino acid derivatives into the corresponding free P(III) amino ester, oxide, sulfide, and notably, complexation to an Au(I) centre. Although this work is focused primarily on the photophysical properties of phosphole amino acids, the demonstration of their Au(I)-coordinating ability combined with the known propensity of phospholes to bind transition metals opens the door for future investigation into phosphole-containing peptides both for their fluorophoric and metal-binding characteristics.

2.5. Phosphinite amino acids

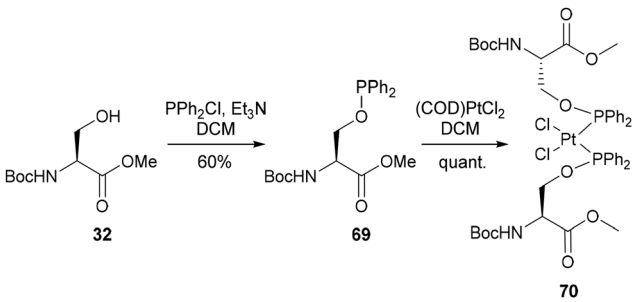
The phosphinite group can be represented as PR_2OR, where the P(III) centre is bonded to one oxygen atom, and two alkyl or aryl groups. In the context of transition metal catalysis, this functionality has proven particularly prevalent in the design of iridium catalysts,[42] with examples including iridium bis(phosphinite) pincer complexes for alkane transfer dehydrogenation,[43] and pyridine–phosphinite ligands for the asymmetric hydrogenation of olefins.[44] Whilst amino acids have been utilised as important chiral starting materials for the synthesis of phosphinite ligands, for example, the use of prolinol-based amidophosphine–phosphinite ligands in Rh-catalysed asymmetric hydrogenation reactions,[45a,b] this class of ligand has scarcely been explored in the context of metal-binding peptides. In 2003, Kraatz and co-workers detailed the first preparation of phosphinite-containing amino acids, based on the modification of sidechain hydroxyl groups. Treatment of Boc-protected serine methyl ester **32** with chlorodiphenylphosphine under basic conditions afforded the corresponding phosphinite **69** in 60% yield (Scheme 15) which coordinated in a 2 : 1 ratio with Pt(II) to form complex **70**.[46] Additional phosphinite analogues based on the hydroxyl-containing amino acids threonine and tyrosine were also prepared using this method, each of which were demonstrated to coordinate to Pt(II) and Pd(II) ions with square planar geometry. Later work by the same group found Pd complexes with peptide ligands comprising of similar phosphinite amino acids were effective in catalysing asymmetric Heck reactions between iodobenzene **71** and dihydrofuran **73** with up to 98% ee reported (Scheme 16).[47]

2.6. Phosphorylated amino acids

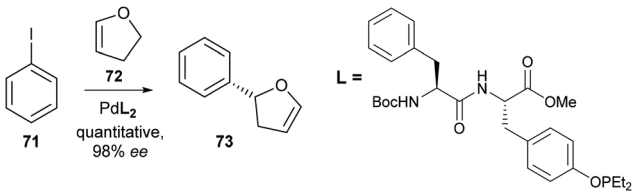
With critical roles across a wide array of cell-signalling processes, phosphorylation has been indicated to be the most commonly occurring post-translational modification (PTM) in the eukaryotic proteome.[48] In metalloproteins, phosphorylation of particular amino acid residues often modulates both the metal binding affinities and the overall properties of the protein as a whole,[49a,b] both from the local effect of altered residue charges alteration and metal coordination geometry, and global conformational changes to the protein that may distort metal-binding sites or expose sites previously



Scheme 14 Synthesis of *N*-protected phospholyl(borane) amino esters – Cavelier and co-workers.[41]



Scheme 15 Synthesis of a serine-derived phosphinite ligand and its coordination to Pt(II) – Kraatz and co-workers.[46]



Scheme 16 Asymmetric Heck reaction catalysed by a Pd(II) complex containing the dipeptide phosphinite ligand Boc–Phe–Tyr(OPEt$_2$)OMe – Kraatz and co-workers.[47]

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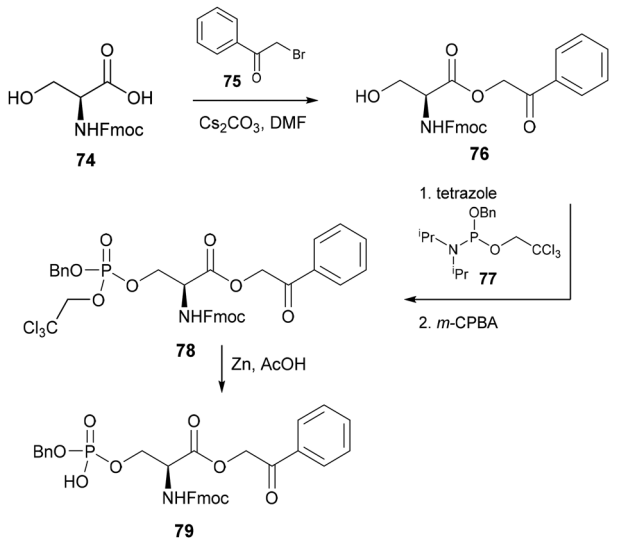
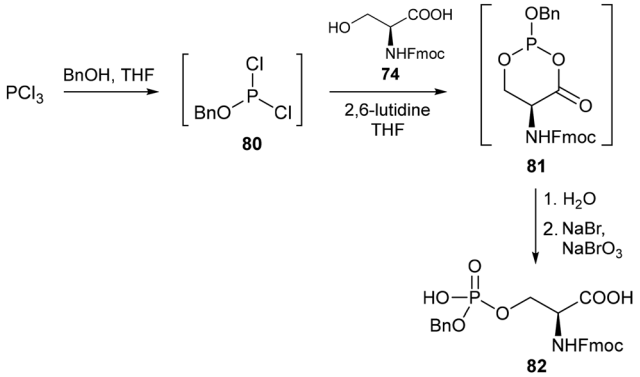
occluded.[50] A prominent example of such a protein is α-synuclein, a metal-binding protein found primarily in the brain and an important hallmark of Parkinson's disease pathology. Several studies have probed the impact of Ser and Tyr hydroxyl group phosphorylation in the C-terminal region of α-synuclein, reporting profound effects on the peptide's metal binding affinity and specificity,[51a,b] as well as the conformation and location of the peptide's metal-binding sites.[52] Given the inaccessibility of commercially available phosphorylated amino acids, reliable methodology for their preparation is of significant demand for the study of metalloprotein phosphorylation events.

First reported by Wakamiya and co-workers in 1994, the original synthesis of phosphorylated serine **79** involved the reaction of phenacyl-protected serine derivative **76** with dialkyl *N*,*N*-phosphoramidite **77** in the presence of tetrazole to form the phosphite intermediate **78**, which was ultimately converted to the desired phosphoamino acid **79** following oxidation with *m*-CPBA and removal of the phenacyl and trichloroethyl groups (Scheme 17).[53]

As a more efficient alternative to the established phosphoramidite-based approach, Bakale and co-workers reported a one-pot synthesis of protected phosphoserine derivatives involving convenient *in situ* generation of the phosphorylating agent whilst removing the need for tetrazole, a highly explosive heterocycle used for the promotion of phosphitylation.[54] The reaction of phosphorus trichloride with benzyl alcohol gave rise to **80**, which was sufficiently reactive towards the serine hydroxyl group without the use of a tetrazole activator, after which the resulting cyclic mixed phosphite intermediate **81** was subsequently oxidised into the target phosphorylated amino acid **82** (Scheme 18). Further development of this method gave rise to a procedure enabling the synthesis of Fmoc-*O*-benzyl-L-phosphoserine on a kilogram scale.[55]



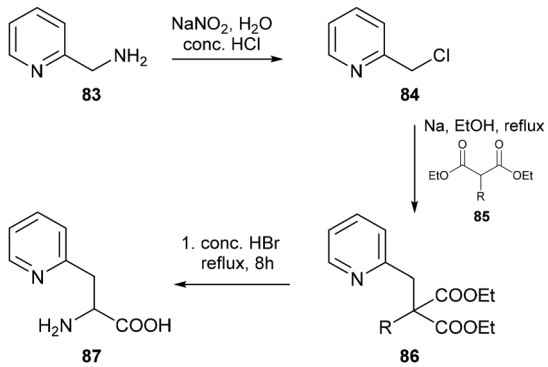
Scheme 17 Synthesis of phosphorylated serine **79** using phosphoramidite chemistry – Wakamiya and co-workers.[53]



Scheme 18 One-pot process for the synthesis of phosphoserine derivatives – Bakale and co-workers.[54]

3. Metal coordination *via* nitrogen

In the context of metal coordination, N-donor ligands represent a vast range of compounds with diverse properties. The pyridine ring is an example of a highly pervasive structural motif across transition metal catalysis, owing both to the availability of its nitrogen lone pair for metal coordination and to the overall stability of its planar ring structure. In ligand design, pyridine is commonly found within an extended conjugated system, *e.g.* bipyridine or phenanthroline, or as part of a mixed heteroatomic ligand such as pyridine-oxazolines (PyOx). Due to the growing prominence of artificial metalloenzymes and other peptide-based catalysts, reliable methodology for incorporating metal-binding functionalities into peptides is of great interest. Accordingly, numerous examples of unnatural amino acids with such functionalities have emerged in the literature for various applications such as the design of metal ion sensors and the study of electron transfer in peptides.[56a,b] Given the wide range of N-donor ligand architectures that have been incorporated into the design of noncanonical amino acids, this section has been organised into further subcategories based upon structural features, namely denticity and the aromatic or aliphatic nature of the ligand (Scheme 19).



Scheme 19 Synthesis of 2-pyridylalanine **87** *via* the malonic ester method, where R = pthalamido, benzamido or acetamido.

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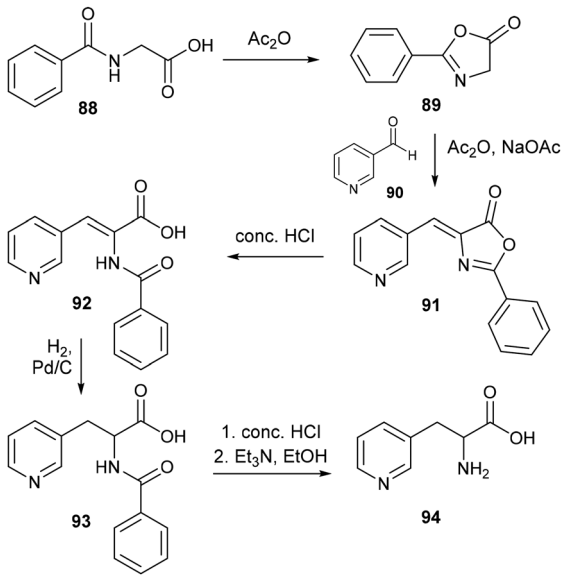
3.1. Pyridylalanine derivatives

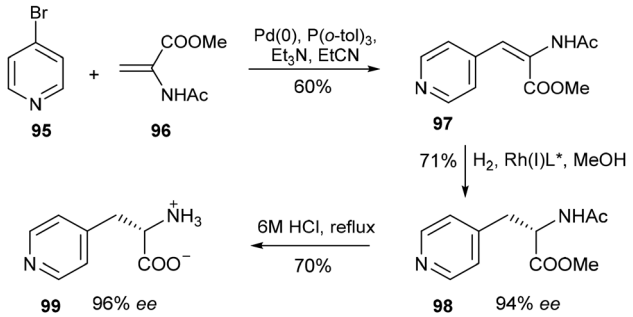
Early syntheses of pyridylalanine derivatives typically relied upon one of two approaches: synthesis *via* a malonic ester (Scheme 19) or *via* an azlactone intermediate (Scheme 20). The former method involves alkylation of an amido-functionalised malonic ester (**85**) at the α-carbon position using picolyl chloride **84**, readily accessible from the corresponding amine **83**, followed by acidic hydrolysis under reflux to access the desired amino acid **87** from the condensation product **86**, as shown in Scheme 19. The earliest synthesis of a pyridyl-functionalised alanine derivative was reported by Overhoff and coworkers in 1936, who first isolated 2-pyridylalanine as a racemate.[57] Subsequent efforts towards increasing both the yield and scale of the synthesis included replacement of the original pthalimidomalonic ester with benzamido- or acetamido-malonic esters, use of ethanol instead of xylene as a solvent for the condensation reaction, and refluxing with hydrobromic *versus* hydrochloric acid as originally reported by Overhoff.[58a,b] The applicability of the 2-pyridylalanine derivative prepared *via* this method for peptide synthesis was later demonstrated by Watanabe and coworkers in 1968, who successfully isolated the corresponding dipeptide benzyl ester in 75% yield upon carbobenzoxylation of 2-pyridylalanine and subsequent amide coupling to glycine benzyl ester using dicyclohexylcarbodiimide.[59]

Comparatively, methodology for synthesizing pyridylalanines *via* an azlactone intermediate has experienced greater development. Based upon the well-known Erlenmeyer synthesis of aromatic amino acids,[60] the azlactone method involves firstly the formation of 2-phenyl-oxazolone **89** from *N*-benzoylglycine **88**, which cyclises in the presence of acetic anhydride and a fused sodium acetate catalyst – this reactive intermediate then undergoes condensation with an aromatic aldehyde **90** to form the azlactone species **91** as shown in Scheme 20. For both methods, acidic hydrolysis is used to access the desired amino acid from the condensation product, while the azlactone approach additionally requires catalytic hydrogenation to reduce the enamide bond still present in the acrylic acid **92** prior to hydrolysis. The azlactone method was first applied to the synthesis of 3-pyridylalanine by Wibaut and coworkers in 1955,[61] who obtained the racemic amino acid in up to 68% yield, albeit on a relatively small, sub-gram scale. This method was soon extended to access the isomeric 2- and 4-pyridylalanines,[62] while modification to the original reaction conditions in subsequent reports led to improved outcomes,[63] such as the introduction of anhydrous potassium carbonate as a catalyst for azlactone formation, which ultimately enabled the gram scale synthesis of DL-3-pyridylalanine in 95% yield.[64]

In 1984, Cativiela and coworkers incorporated chiral phosphine-containing rhodium complexes in the synthesis of 3-pyridylalanine among various hetaryl-functionalised amino acids.[65] In this work, prochiral acetamido-hetarylacrylic acids were formed upon hydrolysis of the azlactone condensation product of the corresponding hetaryl-aldehyde with *N*-acetyl- or benzoyl-glycine – these prochiral precursors were then subjected to Rh-catalysed hydrogenation to generate 3-pyridylalanine with moderate enantioselectivity. A similar approach was later taken by Döbler and coworkers in 1996, who used a rhodium catalyst in the presence of HBF_4 to form enantiomerically pure 3- and 4-pyridylalanines in up to 90% ee.[66] A variation of this method was reported by Bozell and coworkers, who synthesized enantiopure pyridylalanines *via* a Heck-like Pd-catalysed coupling of 4-bromopyridine **95** with olefin **96** (Scheme 21), followed by Rh-catalysed asymmetric hydrogenation and acidic hydrolysis.[67] Although initial attempts using conditions originally reported by Heck[68] led to the undesired bipyridyl homocoupling product, implementation of more dilute reaction conditions gave the prochiral enamide **97** which was subsequently converted to the L- or D-enantiomers of 4-pyridylalanine (**99**) in up to 96% ee. While no analogous asymmetric syntheses have emerged from the malonic ester methods, enantiopure pyridylalanines have been obtained in conjunction with either azlactone or malonic ester approaches through the use of enzymatic resolution *via* subtilisin[69] or chymotrypsin.[70a–c]



Scheme 20 Synthesis of 3-pyridylalanines *via* the azlactone method.



Scheme 21 Asymmetric synthesis of L-4-pyridylalanine – Bozell and co-workers.[67]

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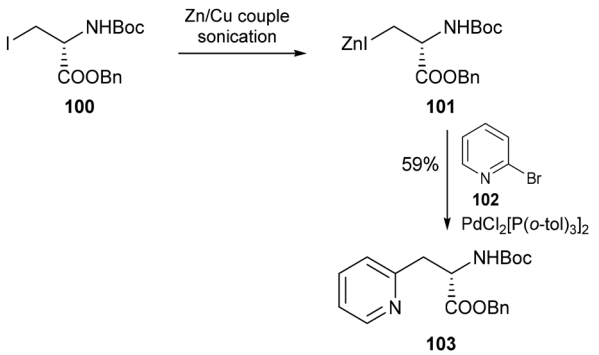
A growing number of methods have since emerged for the incorporation of pyridyl moieties into amino acid scaffolds. One widely utilised strategy is the used of the Negishi cross-coupling, a C–C bond forming reaction pervasive across synthetic chemistry. The application of this reaction to the area of amino acid synthesis was pioneered by Jackson and co-workers in 1989.[71] In their seminal report, an organozinc reagent derived from Boc-protected iodoalanine was demonstrated to effectively undergo palladium-catalysed coupling to a variety of aryl iodides to generate enantiomerically pure β-aryl amino acids. The scope of the transformation was additionally extended to include heteroaryl halides such as 2-bromopyridine (**102**) to give the corresponding β-(2-pyridyl)alanine **103** in 59% yield, alongside numerous further examples containing substituted pyridines which were used in the construction of catalytic tripeptides (Scheme 22).[72] Since this first report, Negishi cross-coupling has been widely applied to the synthesis of pyridyl-containing amino acids, with examples including the antitumour antibiotic azatyrosine,[73a,b] the chloroazatyrosyl napthoamide fragment of the kedarcidin chromophore,[74] and tridentate 2,6-bis(ethoxycarbonyl)pyridin-4-yl alanine ligands.[75] An in-depth discussion of the use of Negishi cross-couplings for the synthesis of unnatural amino acids can be found in a previous review by Brittain and Cobb.[76]

Other synthetic routes that have been employed for the synthesis of pyridylalanine derivatives include the alkylation of chiral glycine equivalents with pyridyl halides[77] or carbinols[78] followed by acidic hydrolysis, photoredox-catalysed radical conjugate addition of halopyridines to dehydroalanine,[79] and a two-step strategy comprised of a lanthanide-catalysed hetero Diels–Alder and subsequent Knoevenagel-Stobbe reaction.[80] Additionally, several reports have detailed the use of a chemoenzymatic approach to access unnatural amino acids with high enantioselectivity. In particular, the enzyme phenylalanine ammonia lyase (PAL) has emerged as an effective biocatalyst for the synthesis of L-pyridylalanine analogues. In 2016, Turner and co-workers reported a one-pot telescopic synthesis comprising of two steps: firstly a Knoevenagel-Doebner condensation between a substituted pyridyl–aldehyde and malonic acid in the presence of piperidine to form the corresponding pyridylacrylic acid, followed by biocatalytic hydroamination using bacterial PAL from *Anabaena variabilis*.[81] Notably, this biocatalyst offered conversions of up to 95%, and excellent enantioselectivity of >99% ee. The use of other PAL enzymes as well as a tyrosine phenol lyase have also been documented for the biosynthetic synthesis of pyridylalanine derivatives.[82a–c]



Scheme 22 Synthesis of β-(2-pyridyl)alanine *via* palladium-catalysed cross coupling of the organozinc reagent **100** with 2-bromopyridine **101** – Jackson and co-workers.[72]

In contrast with the aforementioned pyridylalanines, very few examples have been reported of analogous glycine derivatives, *i.e.* where the pyridyl moiety is attached to the amino acid *via* the α-carbon. Although several syntheses of N-terminally substituted glycine derivatives have been reported,[83a–c] strategies towards a pyridylglycine derivative suitable for peptide synthesis have remained sparse in the literature. In 2006, Gerhardt and Weck detailed the design of a series of self-assembling biological-hybrid scaffolds comprised of a *p*-methoxy SCS–Pd complex coordinated to a tripeptide bearing a central pyridylalanyl or pyridylglycyl residue.[84] While synthesis of the pyridylalanine-containing tripeptide posed no issues, installation of the pyridylglycine moiety proved problematic due to the susceptibility of the pyridylglycyl carboxylic acid to spontaneous decarboxylation. To circumvent this issue, they proposed synthesizing a stable dipeptide unit containing a protected 3- or 4-pyridylglycine moiety, which could then undergo further amide coupling to facilitate peptide extension. Their approach involved a method based on a modified Strecker, Ugi-type four-component synthesis developed by Kunz and co-workers,[85a–c] where the pyridine carboxaldehyde precursor **104** is reacted with protected amino sugar auxiliary **105** to form an imine intermediate (Scheme 23) which subsequently undergoes attack by isonitrile **106** and methanoic acid. Following acidic hydrolysis of the resulting dipeptide **107** to liberate the N-terminal amine, further amide coupling was successfully achieved to give the desired *N*-pthaloyl-, *C*-methyl ester protected tripeptide **109**. The pyridyl-containing peptides were subsequently coordinated to a complementary recognition unit comprised of a SCS–Pd pincer complex (**110**). While previous examples of pincer amino acids featured an N-terminal metal-binding moiety,[86] limiting their versatility as functional synthons for the construction of supramolecular peptide-based architectures, the design of **108** conveniently enables further coupling to either terminus of a growing peptide.

In 2016, Marsden and co-workers reported a synthetic route to α-pyridyl, α-substituted amino acids of type **114** (Scheme 24).[87] Based upon recent reports from Londregan and co-workers involving the PyBroP-activated reaction of pyridine *N*-oxides with a range of nucleophiles,[88a–c] the authors reasoned that azlactones of comparable pK_a[89] such as **112** may serve as suitable nucleophiles for reaction with activated electrophile pyridine *N*-oxide **113**, giving access to amino acids **114** *via* a direct pyridylation approach. With the aim of using greener reaction conditions, ethyl acetate was found to enable the reaction with efficiency comparable to that of THF, when used in conjunction with TsCl as an activating agent.

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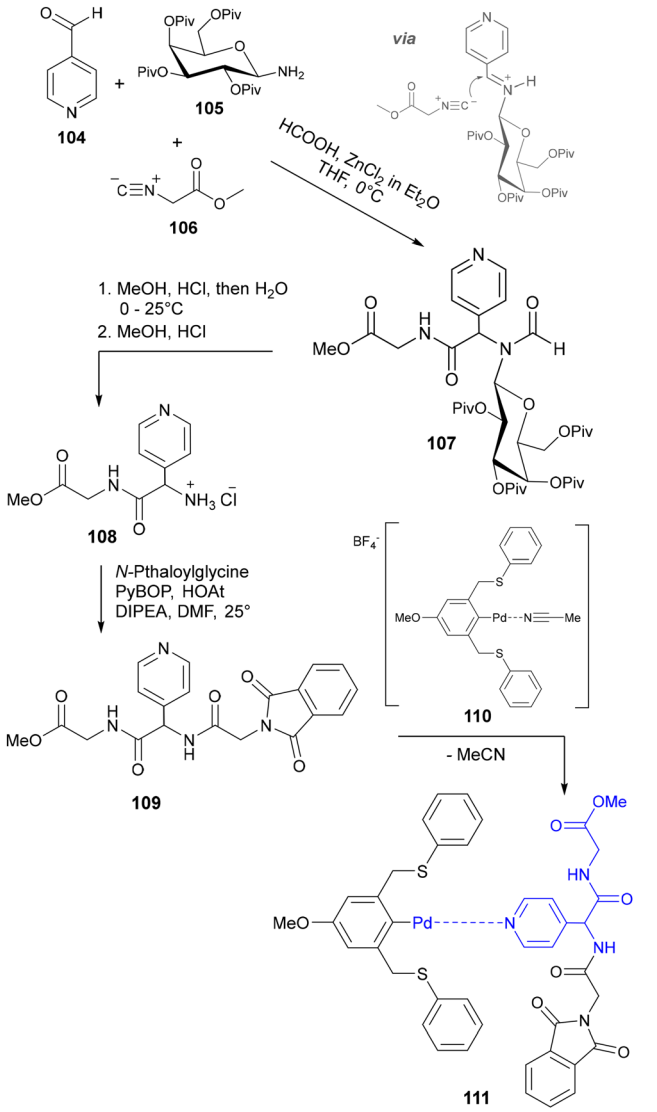
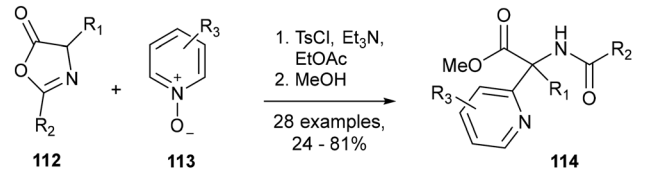


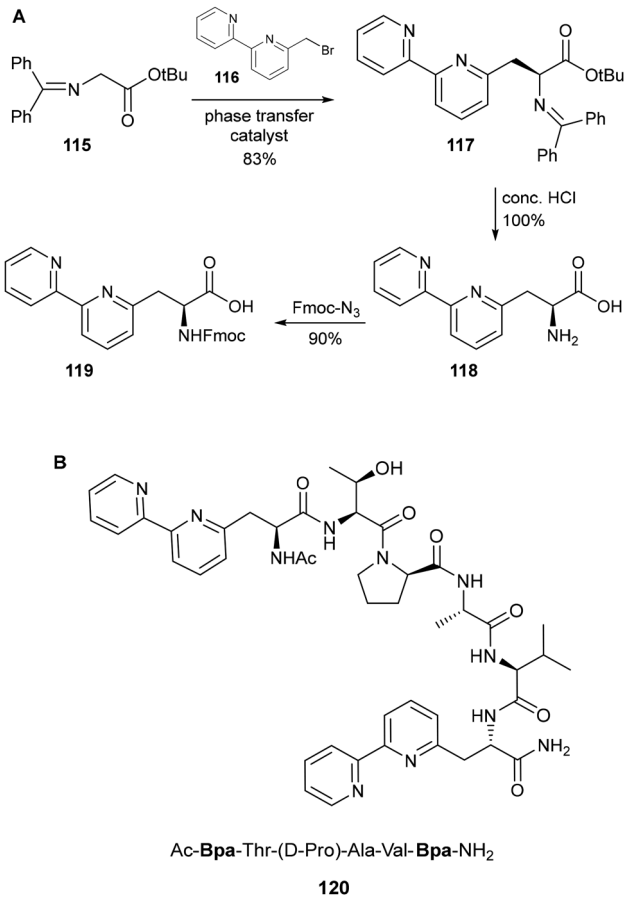
Scheme 23 Synthesis and incorporation of 4-pyridylglycine residue into a peptide for binding to a palladium pincer complex – Gerhardt and co-workers.[84]



Scheme 24 Synthesis of α-pyridyl, α-substituted amino acids – Marsden and co-workers.[87]

3.2. Bipyridyl- and extended pyridyl-amino acids

The first example of a bipyridyl-functionalised amino acid was reported in 1992 by Imperiali and coworkers, who synthesized Fmoc-protected bipyridin-6-yl **119** starting from the commercially available benzophenone imine glycine derivative **115** (Scheme 25A).[90] Using a method previously reported by O'Donnell for the synthesis of α-amino acids,[91] asymmetric alkylation of **115** with 6-(bromomethyl)-2,2′-bipyridine **116** was achieved using a *N*-benzylcinchonidinium chloride phase transfer catalyst, giving the *S* enantiomer of **117** with a moderate ee of 53%. Following crystallisation to resolve the racemate, enantiomerically pure **117** was hydrolysed under acidic conditions to afford the free amino acid **118**. Fmoc azide was used for installation of the amine protecting group, enabling direct use of **119** as a building block for the solid-phase synthesis of metallopeptides. By incorporating either one or two (Scheme 25B) bipyridin-6-yl moieties into the peptide, alongside a β-turn-favouring D-proline residue, the relative contributions of both inter- and intramolecular coordination towards metal binding could be investigated. Standard spectroscopy methods were used to evaluate the interactions between these peptides and a series of divalent metal cations: UV-Vis titrations were used to derive a series of metal–peptide dissociation constants, while spectra obtained by circular dichroism indicated the formation of a chiral complex upon addition of Cu^{2+} to peptide **120**.[92]



Scheme 25 (A) Synthesis of the 6-bipyridyl-containing amino acid **6Bpa** and (B) structure of a peptide incorporating the **6Bpa** residue – Imperiali and co-workers.[90]

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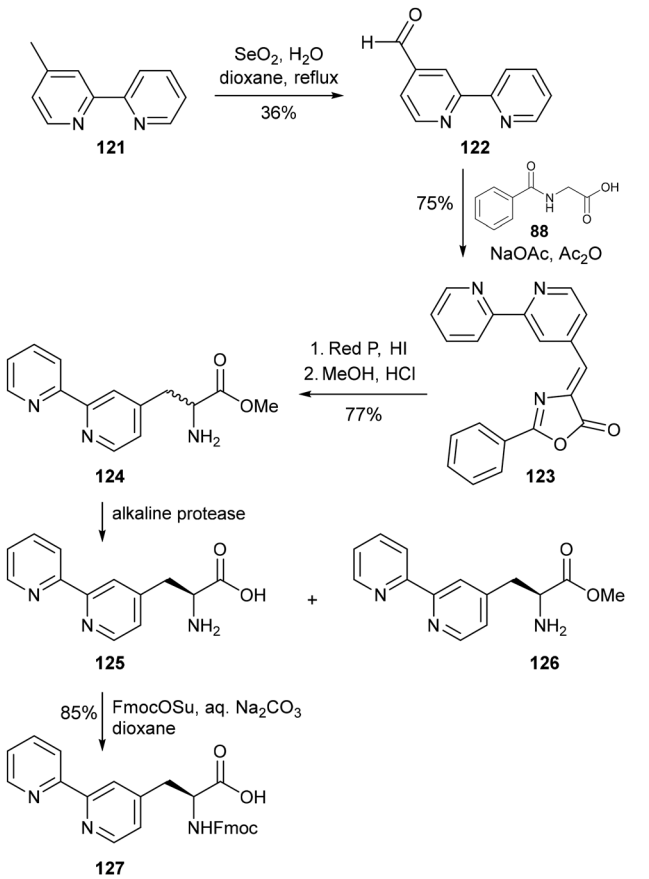
Given the sizable impact of varying bipyridine ring substitution on the metal binding properties of a bipyridyl ligand, Imperiali and coworkers sought to develop a means of accessing the bipyrid-4-yl and 5-yl isomers of **6Bpa**. Racemic **5Bpa** was obtained using the previously reported asymmetric alkylation approach (Scheme 26), using 5-(bromomethyl)-2,2′-bipyridine with the same commercially available glycine derivative and phase transfer catalyst.[93] Synthesis of the bipyrid-4-yl derivative **127** was carried out *via* a route based on the Erlenmeyer synthesis of aromatic amino acids reported in 1893.[60] Treatment of the unsymmetrical bipyridine **121** with selenium dioxide enabled transformation of the 4-methyl group to the corresponding formyl group of aldehyde **122**. Reaction of **122** with *N*-benzoyl glycine (**88**) generates a benzamide intermediate, which undergoes cyclisation in the presence of acetic anhydride to give oxazolone **123**. Simultaneous reduction and hydrolytic cleavage of the oxazolone moiety using hydroiodic acid with red phosphorus afforded the desired racemic amino acid, which was converted to the corresponding methyl ester **124** by treatment with methanol under acidic conditions. Unlike with bipyridin-6-yl **119**, enantiomerically pure material could not be obtained by crystallisation for the 4Bpa and 5Bpa derivatives. Instead, resolution was achieved enzymatically using a previously reported method for the enantioselective hydrolysis of racemic amino acid esters,[94] in which a mixture of enzymes is used with the alkaline serine protease Subtilisin Carlsberg as the major component.



Scheme 26 Synthesis and enzymatic resolution of the 5-bipyridyl-functionalised amino acid **5Bpa** – Imperiali and co-workers.[93]

The Imperiali group subsequently used amino acids **119** and **127** to enable the construction of mutant horse heart cytochrome c (hh cyt *c*) proteins containing a redox-active Ru^{2+} centre.[95] The native heme-containing fragment (residues 1–65) was obtained from the wildtype protein by cyanogen bromide cleavage at Met65, resulting in the formation of a C-terminal homoserine lactone functionality, while the second fragment, containing either **6Bpa** (**119**) or **4Bpa** (**127**) at the 72 position, was assembled on solid phase. Incubation of the two purified fragments under neutral reducing conditions enabled amide bond formation between the C-terminal lactone and N-terminal amine. Treatment of the resulting proteins with excess $Ru(bpy)_2CO_3$ gave rise to metal complexes of the 4Bpa- and 6Bpa-modified proteins, which demonstrated significantly increased rates of electron transfer *via* direct photoinduced (DP) and flash quench (FQ) techniques when compared with an analogous His72 cyt *c* mutant. Use of the 5-pyridyl amino acid was later reported by Yoshikawa in 1996 for the design of a Ni^{2+}-binding 3α-helix bundle: placement of **5Bpa** in the middle of a 13mer peptide with flanking hydrophobic cyclohexylalanine (Cha) and leucine residues promoted the formation of a tight hydrophobic core, which, upon assembly of the 3α-helical structure, would in turn surround the hydrophilic trisbipyridine nest, in which the Ni^{2+} ion is accommodated.[96]

Following Imperiali's original syntheses of bipyridinyl α-amino acids, Bowler and coworkers desired a simplified method for making an amino acid attached to the bipyridine ring *via* the 4 position that avoided the use of selenium dioxide, as well as the laborious need to construct the bipyridine ring system.[97] The first step involved formation of bipyridine **129** *via* asymmetric bromination of commercially available 4,4′-dimethyl-2,2′-bipyridine **128** using *N*-bromosuccinimide (Scheme 27). The brominated bipyridine was then converted into the desired amino acid **132** in an analogous fashion to the original method:[90] treatment with the glycine benzophenone imine derivative **115** and phase transfer catalyst, subsequent acidic hydrolysis and esterification of **130**, with enzyme-mediated resolution bringing the final enantiomeric excess up from 65% to 95%. Boc-protected **132** facilitated the formation of an α-helix secondary structure upon SPPS installation into a predominantly alanine-containing peptide.

Seeking to expand the repertoire of amino acids with side-chain N-heterocyclic scaffolds Imperiali and coworkers reported the synthesis of α-amino acids containing phenanthroline and 2,9-dimethyl-1,10-phenanthroline (neocuproine) functionalities for incorporation into small peptides.[98] Applying methodology previously reported by Sörensen,[99] chloromethyl derivatives **133a–b** were converted into **135a–b** by reaction with excess diethyl acetamidomalonate (**134**) in ethanol under reflux (Scheme 28). Subsequent refluxing with concentrated hydrochloric acid and esterification with acidic

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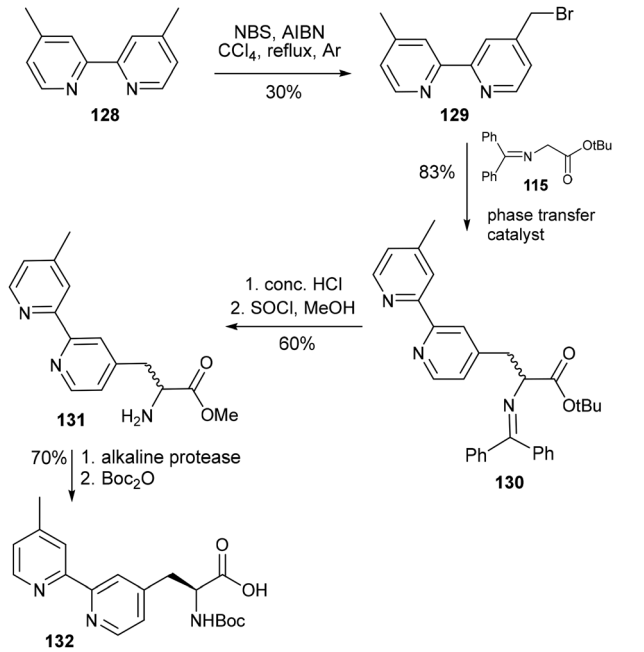
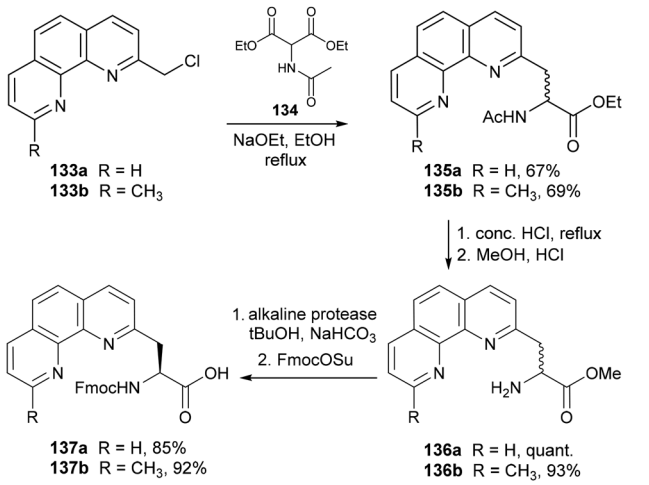


Scheme 27 Synthesis of an *N*-Boc protected 4-methyl-2,2′-bipyridyl amino acid – Bowler and co-workers.[97]



Scheme 28 Synthesis of a phenanthroline-containing amino acid – Imperiali and co-workers.[98]

methanol afforded the phenanthrolyl- and neocuprionyl-amino acid methyl esters **136a** and **136b** respectively. Stereoselective hydrolysis of the racemic methyl esters was achieved using alkaline protease giving the amino acids **137a** and **137b** with >98% ee.

All amino acids discussed thus far have fallen into the category of α-amino acids, meaning that the amino group and side chain R group (in this case, bipyridyl) are attached to the α-carbon *i.e.* the central backbone carbon atom adjacent to the carbonyl carbon of the carboxylic acid group. While the standard proteinogenic amino acids fit into this category, hundreds of other naturally-occurring amino acids exist in which the location of the core amino functional group relative to the alpha carbon is varied. This structural variation is classified using the Greek letters α, β, γ, δ … ω to denote the position of the amine terminus along a carbon chain of increasing length, for example β-phenylalanine **139** and γ-aminobutyric acid **141** – also known as GABA, the most common central nervous system inhibitory neurotransmitter (Fig. 2). The carbon at the final position is sometimes designated lower-case omega (ω) irrespective of chain length. In the context of metal-binding residues, the bipyridine containing **140** (Fig. 2) is therefore classified as an ω-amino acid, in contrast with the α-amino acid **138** containing a sidechain bipyridine moiety. Synthesis of SPPS-compatible amino acids resembling **140** therefore allows for the incorporation of a *N*,*N* bidentate unit into a peptide backbone, in turn unlocking metal-binding architectures with unique three-dimensional characteristics.

Synthesis of this type of bipyridyl amino acid was first reported by Imperiali and coworkers in 1996, who derivatised **146** into the building block **Fmoc-XBp** (**148**) for use in the design of fluorescent peptide-based metal ion sensors alongside a cyanoanthracene fluorophore Fmoc–Flu.[100] The synthesis of **148** initially comprised three key stages: preparation and palladium-catalysed Stille coupling of the triflate and stannane pyridine derivatives **143** and **145**, and reduction of the nitro group *via* catalytic hydrogenation to give **146** – the methyl ester of amino acid **148**. The researchers had intended to protect and introduce the ω-bipyridine amino acid directly into a peptide, however, attempts to install an Fmoc group were unsuccessful even under forcing conditions. Due to the poor reactivity of its anilinic amine, **146** was not considered suitable for solid phase peptide synthesis, hence necessitating further modification: **146** was thus transformed into the pseudo-dipeptide **147** by coupling of Boc–glycine *via in situ* formation of a reactive acyl fluoride intermediate. The desired amino acid **148** was obtained following Boc removal, ester hydrolysis and installation of the Fmoc group (Scheme 29).

This building block (**148**) was in turn compatible with SPPS methodology, as shown by its successful incorporation into the peptide **149**, alongside the cyanoanthracene fluorophore Fmoc–Flu **Q** and fluorescence quencher L-3,4-dimethoxy-DOPA (**Dmd**) shown in Scheme 30. The absence of metal ions, FXR03

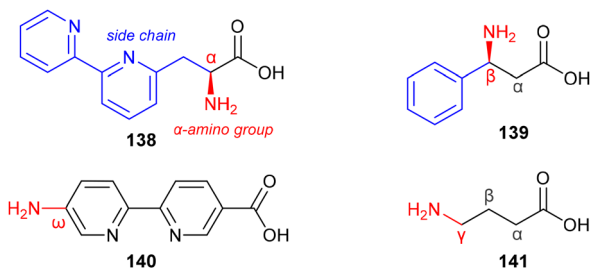


Fig. 2 Classifications of amino acids: bipyridine-containing α- and ω-amino acids Y and X, naturally occurring β- and γ-amino acids A and B.

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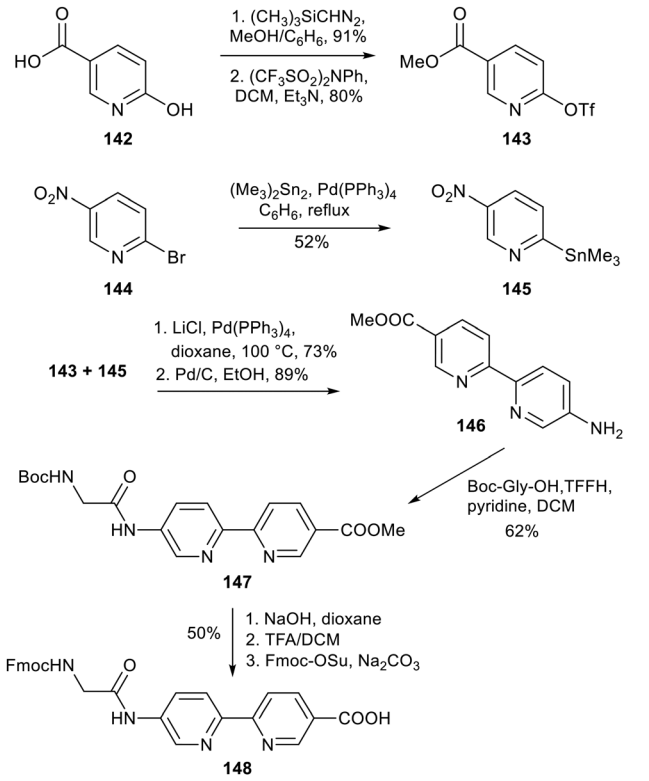
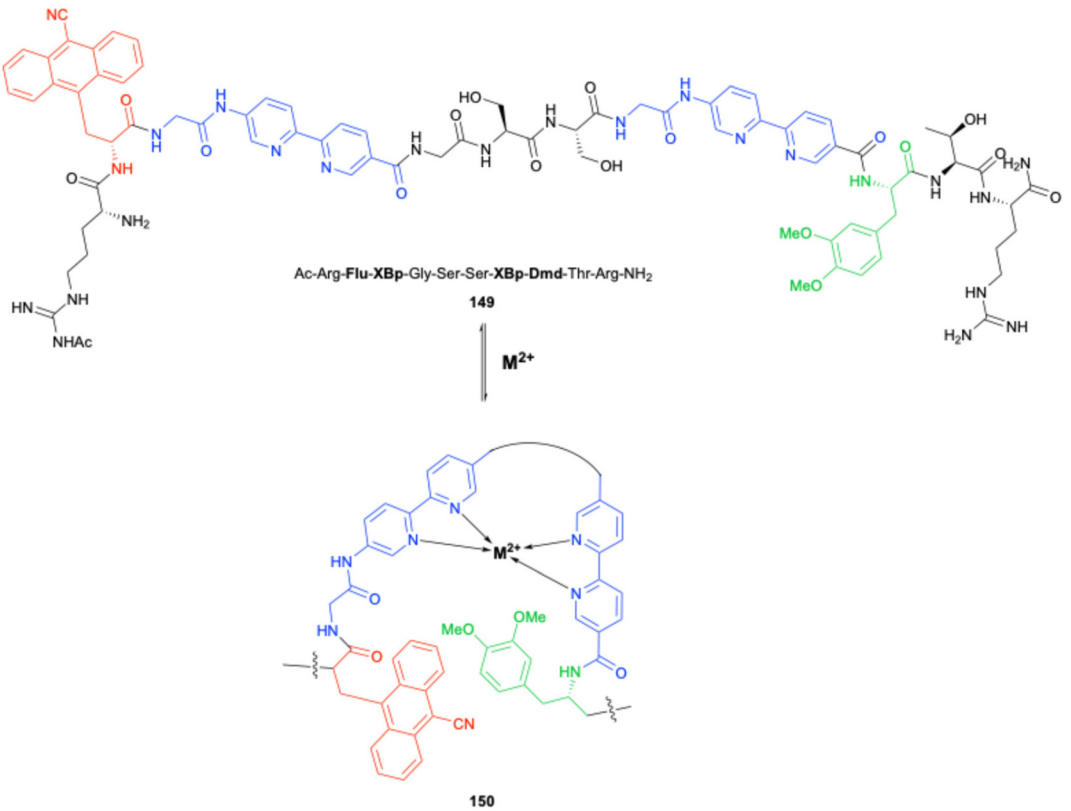


Scheme 29 Synthesis of the ω-amino acid **XBp** containing a bipyridyl group – Imperiali and co-workers.[100]

is found in a random coil conformation and exhibits strong fluorescence on account of the **Flu** sidechain – upon addition of aqueous $ZnCl_2$, binding of Zn^{2+} to the bipyridine units induces a conformational change that brings the fluorescent **Flu** sidechain in close proximity to **Dmd**. This in turn triggers a metal-dependent photoinduced electron transfer (PET) event from the excited state **Dmd** to **Flu**, monitorable by fluorescence emission spectroscopy.

An alternative route to this bipyridyl amino acid was described by Patri and coworkers the following year, starting from the symmetrical ester diethyl 2,2′-bipyridine—5,5′-dicarboxylate **151**, which was converted into **152** by treatment with 1.5 equiv. hydrazine hydrate (Scheme 31).[101] Due to the inherent low solubility of carbohydrazides, it was possible to selectively form the asymmetric monocarbohydrazide (**152**) in 85% yield by adjusting the reaction temperature and the polarity of the ethanol/toluene solvent system. Addition of sodium nitrite to a solution of **152** in concentrated hydrochloric acid converted **152** into the corresponding carbazide **153**, which formed urethane **154** upon Curtius rearrangement. From here, the desired amino acid **155** was finally obtained as the hydrochloride salt by saponification of **154**. A similar Fmoc-protected derivative was reported by Erickson and coworkers in 2000, where the amino acid Fmoc–Abc (**161**) was obtained from 4,4′-dimethyl-2,2′-bipyridine **156** using a selective dual oxidation strategy (Scheme 32).[102] This was achieved



Scheme 30 Metal ion-induced conformational change of a metal-dependent peptide PET sensor; unnatural amino acids with fluorescent, fluorescence-quenching, and metal-binding properties are shown in red, green and blue respectively – Imperiali and co-workers.

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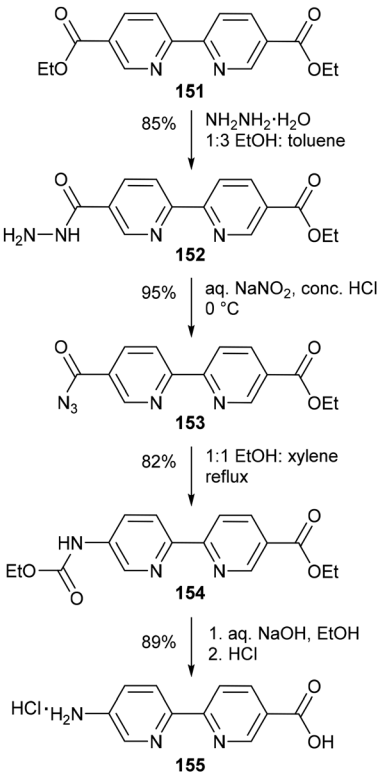
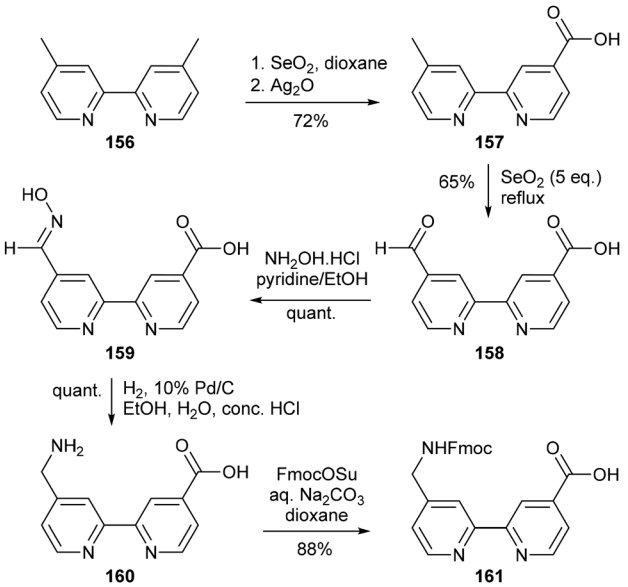


Scheme 31 Synthesis of **XBp** from a symmetrical bipyridine diester – Patri and co-workers.[101]

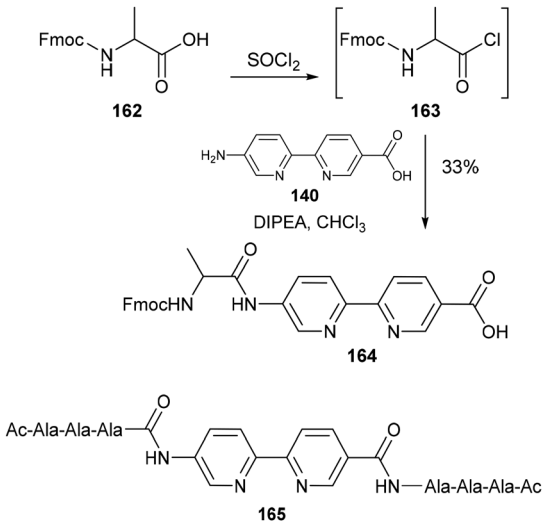


Scheme 32 Synthesis of the bipyridyl amino acid Fmoc–Abc – Erickson and co-workers.[102]

by firstly using selenium dioxide to selectively convert the 4′-methyl group into an aldehyde, followed by oxidation with Ag_2O to access the mono-acid **157** from the monoaldehyde.[103] Subsequent use of selenium dioxide in a fivefold excess enabled oxidation of the remaining methyl group to give **158**, from which the required nitrogen functionality was installed by formation of the oxime **159** followed by catalytic hydrogenolysis to afford the target amino acid **160**.

In 2004, Ishida and coworkers reported the synthesis of a bipyridine amino acid building block for the incorporation into ruthenium-binding peptides.[104] As encountered previously by Imperiali,[100] the poor reactivity of the aromatic amine rendered the amino acid unusable for incorporation with Fmoc peptide chemistry. Accordingly, SPPS installation of bipyridine into a peptide was facilitated using an approach involving condensation of the unreactive amine with an activated intermediate derived from a canonical amino acid, in this case alanine. The route described by Ishida accesses the desired Fmoc-protected **164** through activation of Fmoc-protected alanine (**162**) with thionyl chloride, in turn making the corresponding acyl chloride **163** sufficiently reactive to undergo an amide coupling with the aromatic amine of H–5Bpy–OH (**140**) under basic conditions (Scheme 33). The resulting dipeptide unit (**164**) was introduced into a peptide by standard Fmoc SPPS with HBTU and HOBt as coupling reagents to form the peptide Ac–$(Ala)_3$–5Bpy–$(Ala)_3$–OH (**165**). By using the unprotected bipyridyl amino acid and Fmoc-protected alanine, the overall synthesis is shortened as the need for Boc removal, Fmoc installation and ester hydrolysis is circumvented. This approach was later implemented in the design of an artificial metalloprotein containing a previously unreported ruthenium(II) tris(bipyridyl) complex at the core.[105]

In 2012, an analogous synthesis was reported by the same group, using instead the acyl chloride of Fmoc-protected leucine to couple to the bipyridine amino group (Scheme 34). This ultimately allowed for the construction of a peptide of desired sequence Ac–Ala–Leu–5Bpy–Val–Phe–Gly–NH_2 (**172**) which was subsequently complexed to Ru^{2+} by refluxing the peptide in ethanol with equimolar $Ru(bpy)_2Cl_2$.[106] Shortly



Scheme 33 Preparation of a bipyridyl dipeptide building block for Fmoc peptide synthesis – Ishida and co-workers.[104]

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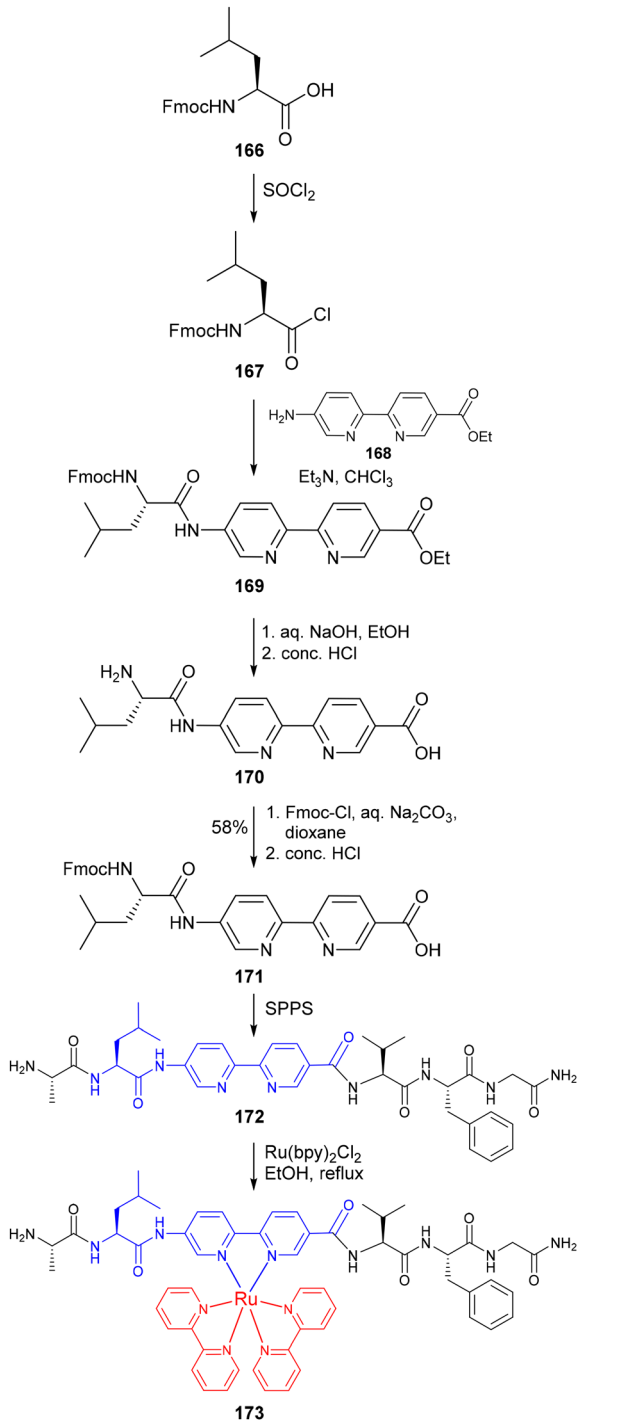
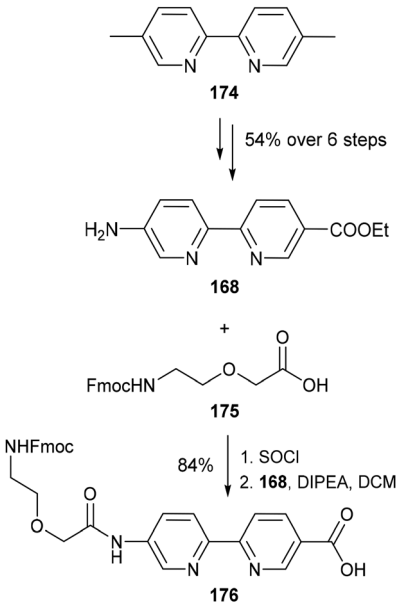


Scheme 34 Incorporation of a bipyridyl dipeptide unit into a peptide for preparation of a ruthenium complex – Ishida and co-workers.[106]

afterwards, the same authors reported the design of Fmoc–O1PenBpy–OH (Scheme 35), another bipyidine-containing building block compatible with SPPS methodology.[107] The bipyridyl unit **168** was synthesized starting from the commercially available 5,5′-dimethyl-2,2′-bipyridine **174** over six steps, and coupled to Fmoc-protected 5-amino-3-oxapentanoic acid



Scheme 35 Synthesis of Fmoc–O1PenBpy–OH – Ishida and co-workers.[108]

(O1Pen **175**) to give the desired product **176** in moderate yield on a multigram scale.

Terpyridines represent another class of nitrogen-containing extended heterocycle that are particularly prominent across the area of transition metal catalysis. Over the past decade, the biocompatibility of the terpyridine (terpy) functionality has been exploited for applications in biocatalysis, with examples including nucleic acid-based catalysts containing Cu(II)–terpy and Fe(III)–terpy functionalities,[109a,b] a terpy–Mn(II) cofactor nitrobindin conjugate with broad oxygenation capabilities,[110] and a terpy–Cu(II) G-quadruplex DNA metalloenzyme for application in enantioselective Diels–Alder reactions.[111] While terpy–metal complexes have been conjugated to genetically encoded proteins for use as catalysts,[112] a report has yet to disclosed of direct incorporation of a terpy amino acid into such a scaffold *via* orthogonalized protein translation, a highly efficient *in vivo* approach for incorporating unnatural amino acids into a protein. This approach has so far only been applied to a small number of chelating amino acids,[113a–c] since the engineering of aminoacyl–tRNA synthetases for this process requires a reliable supply of the unnatural amino acid of interest, which may only be available *via* complex synthetic routes inaccessible to chemical biologists.

In 2019, Budisa and co-workers reported the first synthetic route to a terpyridyl-containing amino acid **185** and its binding properties to a range of bivalent metal ions (Scheme 36).[114] Firstly, the terpyridyl carboxylic acid **180** was synthesized from the corresponding furan-2-yl derivative **179** using a previously reported procedure by Kühn and co-workers,[115] wherein a bis-pyridyl intermediate formed through an aldol condensation of 2-furaldehyde (**177**) with the first equivalent of 2-acetylpyridine (**178**) followed by Michael

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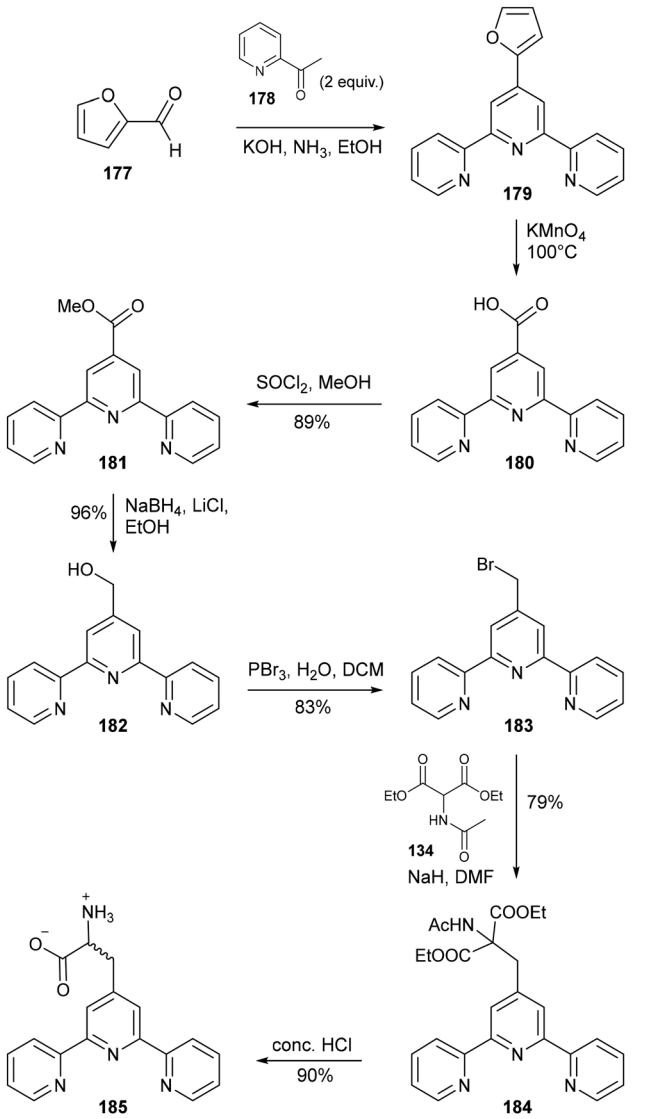
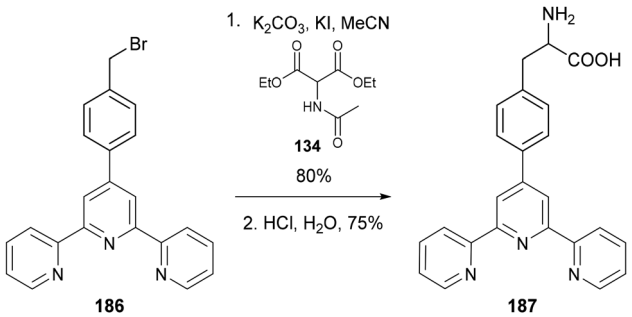


Scheme 36 Synthesis of a terpyridine-functionalised amino acid – Budisa and co-workers.[114]

addition of the second. This approach was later used by Garoufis and co-workers to obtain the multi-aromatic terpyridine-containing amino acid **187** shown in Scheme 37.

3.3. Other pyridyl amino acids

Tripodal ligands are a distinct class of polydentate ligand typically associated with particularly high metal binding affinities. Among a series of other N-donor tripodal ligands, Canary and Chiu first reported the synthesis of bispyridyl glycine residue **188** (Fig. 3) in 2003 *via* the reaction of glycine with picolyl chloride under basic conditions.[116] In 2019, this carboxylic acid was complexed to Pd(II) and conjugated to a transferrin receptor binding peptide sequence *via* the *N* terminus, giving rise to the first example of a Pd(II) metallopeptide with anticancer activity.[117]



Scheme 37 Synthesis of a phenylterpyridyl amino acid – Garoufis and co-workers.

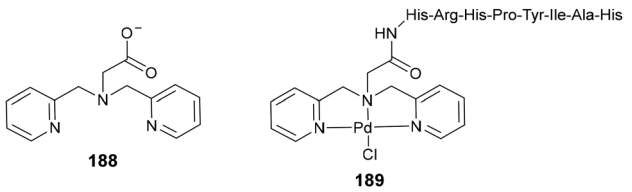
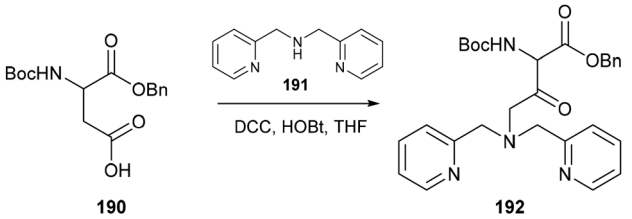


Fig. 3 Bispyridylglycine **A** and a Pd complex of its conjugate to a peptide.

While several other examples of metal-binding amino acid-based polypyridyl ligands and related N-terminally modified metallopeptides exist in the literature,[118a–c] to the best of our knowledge only two examples of an amino acid building block with functional N- and C-termini have been reported. In 2007, Alsfasser and co-workers detailed the design of Boc–Asp(Bpa) OBz **192** by functionalisation of *C*- and *N*-protected aspartic acid with 2,2′-dipicolylamine **191** (Scheme 38).[119] As coordination of the resulting chelating amino acid **192** to Zn^{2+} and Cd^{2+} was shown to sufficiently reduce the rotational barrier of the *N*-Boc amide to permit isomerisation about the C–N bond, amino acid **192** has been proposed for potential applications in the design of metal ion responsive peptide-based conformational switches. Around the same time, König and co-workers detailed the synthesis of several metal-chelating amino acids and peptides,[120] including the lysine derivative **194**, where a dipicolylamine moiety was installed at the ε-amine by reductive amination using $NaBH(OAc)_3$



Scheme 38 Synthesis of an amino acid containing a tripodal dipicolylamine ligand functionality – Alsfasser and co-workers.

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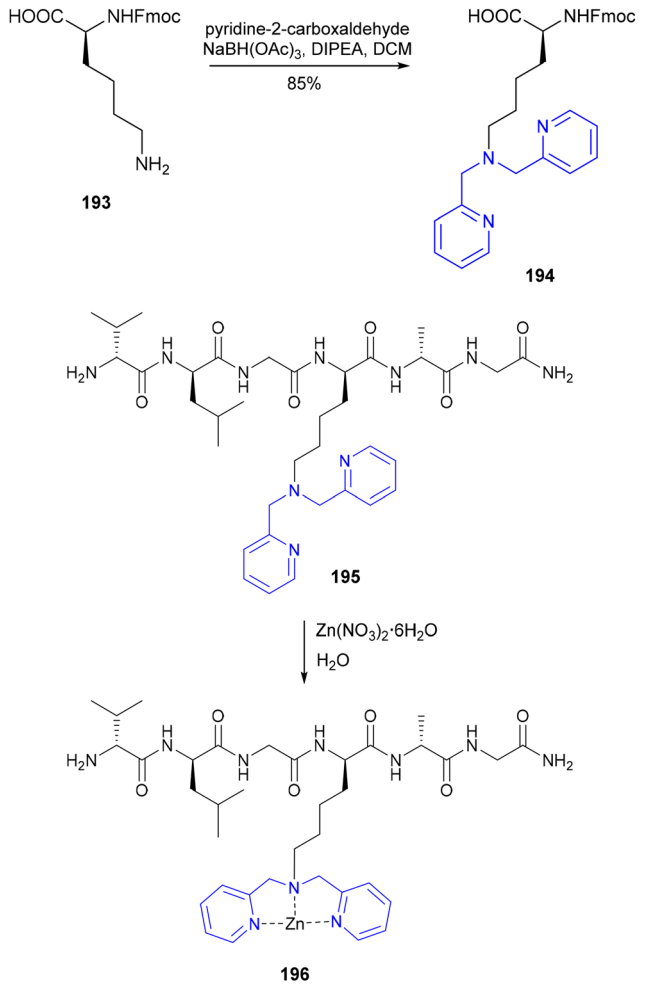
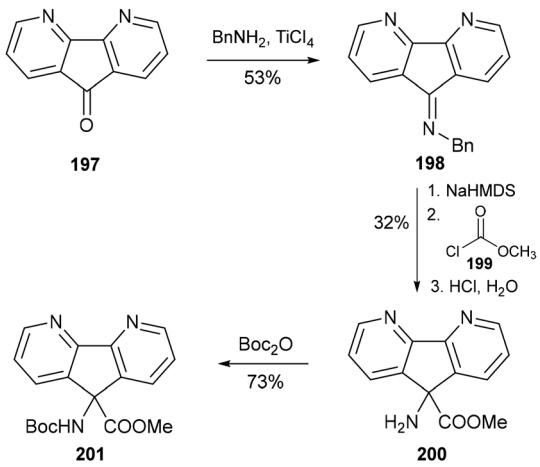


Scheme 39 Synthesis of lysine derivative **194** containing a metal-binding dipicolylamine moiety (highlighted in blue) and its use in the preparation of the Zn^{2+}-binding peptide Val–Leu–Gly-**194**–Ala–Gly–NH_2 – König and co-workers.[120]

(Scheme 39).[121] **194** was incorporated into a peptide using standard SPPS methodology, which formed the Zn^{2+} complex **196** upon stirring with an aqueous solution of a zinc nitrate salt.

Another example of a structurally unique unnatural amino acid is Boc–Daf–OMe **201**, the first reported α-disubstituted glycine derivative containing a rigid bipyridine moiety, synthesized using a transamination–carboxymethoxylation strategy (Scheme 40).[122] Preparation of **201** began with the conversion of the fluorenone **197**, prepared by the oxidation of phenanthroline,[123] into the benzyl-imine **198**. Deprotonation of **198** using NaHMDS followed by addition of excess methyl chloroformate (**199**) effectively introduced a carbomethoxy group at the 9-fluorenyl position, eventually forming the *C*-protected amino acid **200** after acidic hydrolysis. Further installation of a Boc group allowed for coupling of an alanine residue to either terminus of the amino acid,[124] demonstrating the possibility for the use of **201** in the construction of metal-binding peptide architectures.



Scheme 40 Synthesis of an α-disubstituted amino acid functionalised with a rigid 2,2′-bipyridine ligand – Toniolo and co-workers.[124]

4. Metal coordination *via* carbon

4.1. N-Heterocyclic carbene derived amino acids

N-Heterocyclic carbenes, commonly referred to as NHCs, represent an increasingly prominent class of neutral donor ligand. Typically formed upon C2 deprotonation of an *N*-alkylated imidazolium salt,[125a,b] the imidazole-2-ylidene moiety features extensively across the areas of organic synthesis, catalysis, and organometallic chemistry.[126] Considering the nature of its sidechain, histidine has emerged as a convenient precursor for the design of imidazolium-based NHC metal complexes within the area of bioorganometallic chemistry. Given their established affinity towards various metals, several groups have investigated modes of incorporating NHC motifs into peptides as one way of creating artificial metallopeptides. This concept was first investigated in 2005 by Erker and co-workers, who first reported the synthesis of histidine-derived NHC ligands and their complexes to palladium and rhodium.[127] Starting with *N*-and *C*-protected L-histidine, dialkylation of the imidazole nitrogen atoms was initially carried out by treatment with excess Meerwein's reagent ($Et_3O^+BF_4^-$), however this method led to both unwanted *O*-alkylation, as well as racemisation of the desired product. Upon modification of the reaction conditions to instead use *n*-propyl bromide or isopropyl iodide with sodium bicarbonate$_3$, alkylation proceeded cleanly to give di(*n*-propyl)- and diisopropyl-histidinium salts **204** and **205** respectively, both of which were confirmed to be optically active (Scheme 41). To demonstrate their suitability as metal ligands, **204** and **205** were converted into their corresponding Ag(I) complexes with Ag_2O, followed by addition of either $Pd(CH_3CN)_2Cl_2$ or $[RhCl(cod)]_2$ to affect the transmetallation process.

Shortly afterwards, Guillen and co-workers reported a method enabling the introduction of two different alkyl groups at the imidazole nitrogen atoms, also referred to as the wingtip substituents.[128] Using an approach based on the methodology of Cohen and coworkers,[129] histidine methyl

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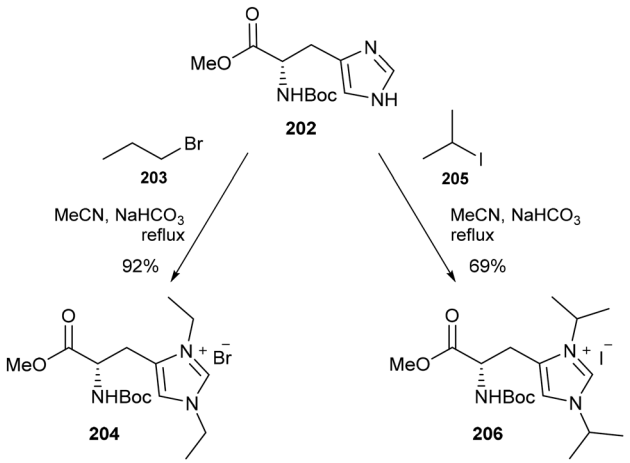
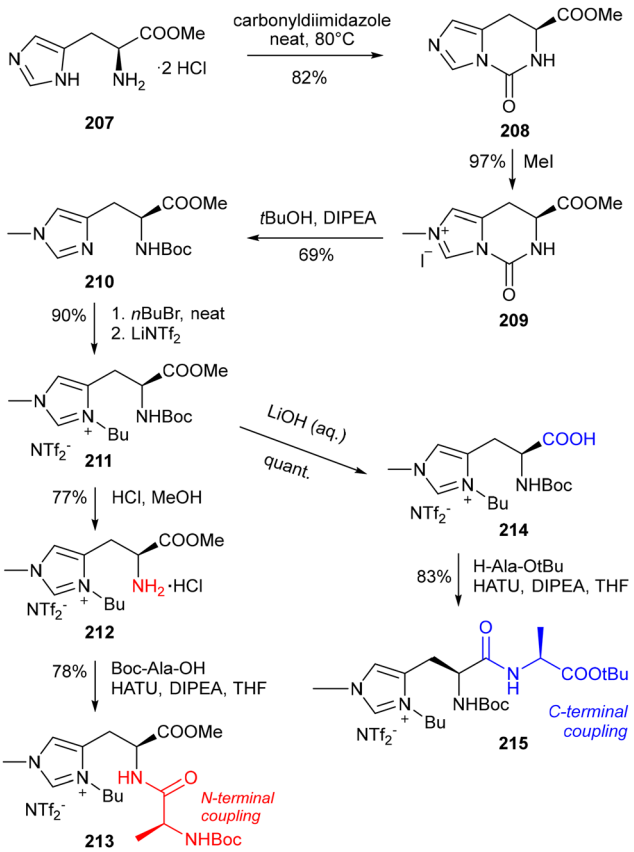


Scheme 41 First reported synthesis of metal-binding imidazolium amino acids from histidine – Erker and co-workers.[127]

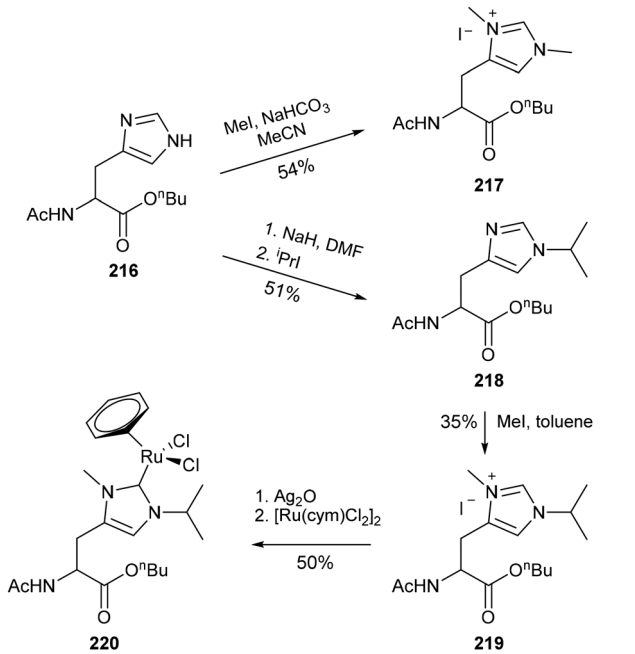
ester was converted into cyclic urea intermediate **208**, wherein both the amino and N2 ring nitrogen atoms are protected, allowing for selective methylation solely at the N1 position (Scheme 42). Subsequent base-mediated ring opening with *tert*-butanol and treatment with *n*-bromobutane gave the desired chiral imidazolium salt **211**. The scope for its application in peptide chemistry was demonstrated by HATU-mediated amide coupling to alanine: acidic hydrolysis of **211** to free amine **212** allowed for coupling to *N*-Boc–alanine, while coupling to the C-terminus was achieved through saponification of **211** into **214** followed by reaction with the *tert*-butyl ester of alanine, ultimately forming dipeptides **213** and **215** without racemization.



Scheme 42 Synthesis and amide coupling of asymmetrically alkylated histidine-derived amino acids – Guillen and co-workers.[128]

Albrecht and co-workers have used similar approaches to synthesize a series of histidine-derived metal-binding ligands with the aim of creating bio-inspired NHC-containing catalysts. Their first report in 2011 detailed a route to symmetrically and non-symmetrically alkylated histidinium salts: *N*,*N*′-dimethylated **217** was formed by refluxing protected L-histidine **216** with excess methyl iodide, while **219** was accessed through selective N_ε alkylation with isopropyl iodide, followed by methylation of the remaining imidazole nitrogen (Scheme 43).[130] These racemic histidine derivatives were subsequently transmetallated to give ruthenium complexes which were shown to exhibit moderate catalytic activity in the transfer hydrogenation of benzophenone.

The following year, the same group reported an enantioselective synthesis of the *N*,*N*′-di-methylated amino acid **222**, using the previously reported methodology of Guillen and co-workers (Scheme 42).[128] This amino acid was then used to form complexes with both iridium and rhodium, the latter of which consistently displayed high conversion in the catalytic hydrosilylation of ketones.[131] Albrecht and co-workers further showed that incorporation of amino acid **222** into the tetrapeptide Boc–Met–Ala–Ala-**X**–OMe (**223**) followed by metalation with $[RhCl(cod)]_2$ gives rise to a macrocyclic chelate (**224**) that can serve as an efficient hydrosilylation catalyst precursor



Scheme 43 Synthesis and ruthenium complexation of racemic histidine derivatives – Albrecht and co-workers.[130]

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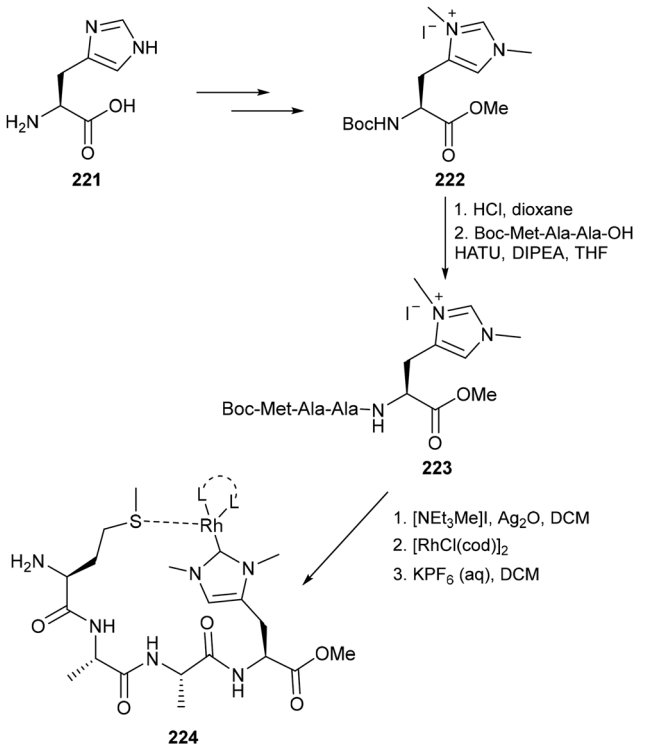
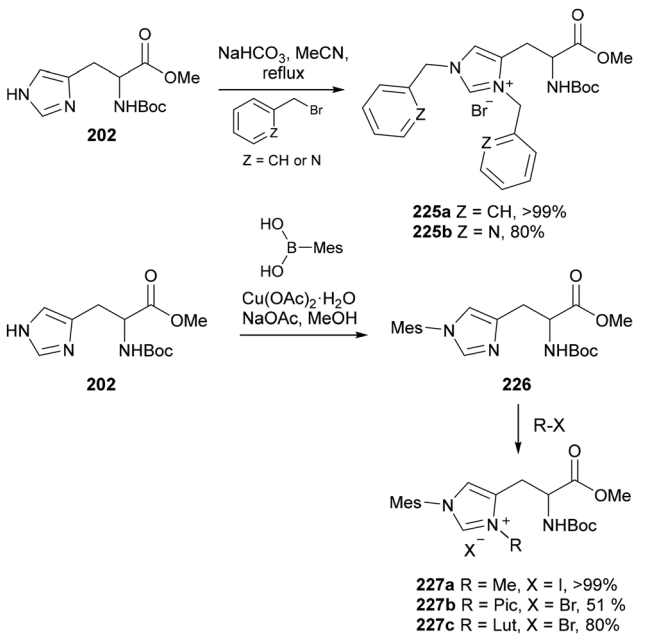


Scheme 44 Enantioselective synthesis of histidine derivative **X** and its incorporation into a chelating peptide for Rh catalysis – Albrecht and co-workers.[132]

(Scheme 44).[132] Comparison with a tri-alanyl histidinium peptide indicated that chelation of a rhodium centre by histidinium and methionine residues *via* a C,S-bidentate binding mode enhances catalytic turnover.[133] In 2021, they reported an Fmoc-protected analogue for use as a building block for solid phase peptide synthesis. Metallation of the resulting peptide scaffold with iridium generated a protein-like assembly furnished with a metal–carbene active site, which displayed pseudo-reductase activity in the hydrogenation of acetophenone.[134]

The amino acids and related catalytic metal complexes discussed so far have only included histidine-derived NHC ligands with simple alkyl wingtip substituents. Given the well-established influence of a NHC ligand's wingtip substituents on the catalytic activity of its corresponding metal complex,[135a–c] it has been reasoned that expanding upon the structural diversity of existing NHC-containing amino acids would broaden their applicability within transition metal-based catalysis. Seeking to expand the diversity of NHC-containing amino acids, Elsevier and co-workers reported new methodology leading to novel benzyl- and aryl-substituted histidinium salts in 2015, which were subsequently investigated as ligands for Pd(II)-catalysed alkyne transfer semihydrogenation.[136] Starting from Boc-protected histidine methyl ester **202**, the symmetrically substituted *N*,*N*-dibenzyl histidinium bromide **225a** was obtained quantitatively through refluxing with benzyl bromide in the presence of sodium bicarbonate. This direct benzylation approach was also used with picolyl bromide; despite the formation of several byproducts, the bis-pyridyl histidinium **225b** was isolated in relatively high yield (Scheme 45). In order to access non-symmetrically substituted derivatives, an adapted version of the Chan–Lam–Evans reaction was used.[137] While attempting *N*-arylation of Cbz-protected histidine methyl ester under original Chan–Lam–Evans conditions was low yielding, Elsevier and co-workers found that the methoxyphenyl and mesityl *N*-arylated histidine derivatives **226** could be accessed in reasonable yield by adapting the improved protocol of Campagne and co-workers,[138] specifically by increasing the reaction times and carrying the reactions out at room temperature. These monosubstituted products were then subject to alkylation with a variety of electrophilic halides, ultimately yielding histidinium salts **227a–c** in yields between 51% and >99% (Scheme 49).

Over the past decade, methodology for the synthesis of NHC-functionalised amino acids has diversified beyond the general approach of alkylated histidine derivatives. In 2014, Gilbertson and co-workers reported the design of **231**, a building block containing both imidazolium and proline moieties, for use in the construction of rhodium complexes of NHC-containing peptides.[139] Starting with *C*- and *N*-protected hydroxyproline **228**, conversion to the corresponding electron-withdrawing triflate **229** created a substrate suitable for the direct quaternisation of *N*-mesityl-substituted imidazole (**230**), ultimately generating the desired amino acid **231** (Scheme 46). The applicability of **231** in peptide synthesis was demonstrated using a standard EDC/HOBt amide coupling protocol at both the C-terminus and proline amine, following removal of the Cbz protecting group, with both the dipeptide **232** and tripep-



Scheme 45 Synthesis of aryl-substituted histidinium amino acids *via* – Elsevier 2015.[136]

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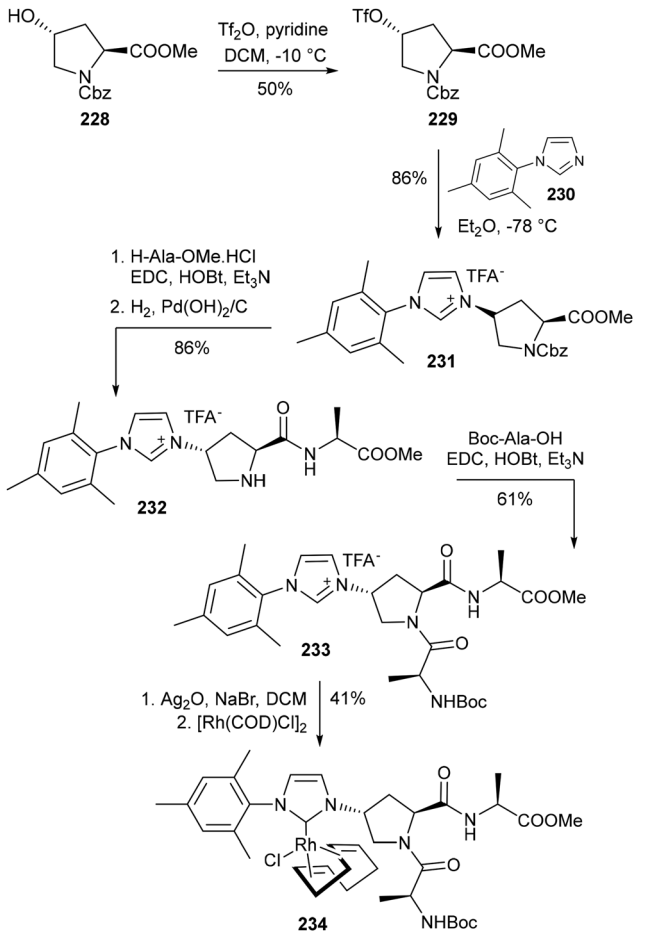


Scheme 46 Synthesis of Rh-binding proline-derived amino acids and peptides – Gilbertson and co-workers.[139]

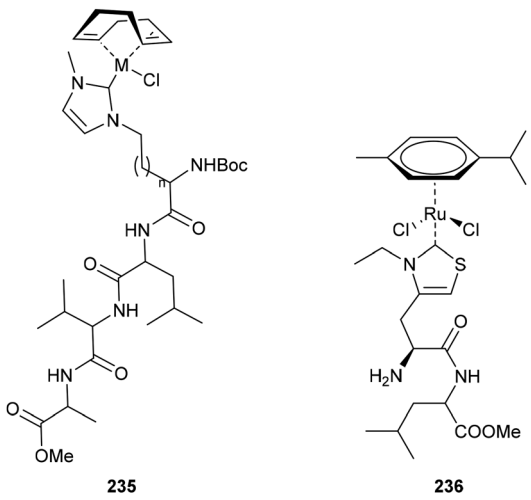
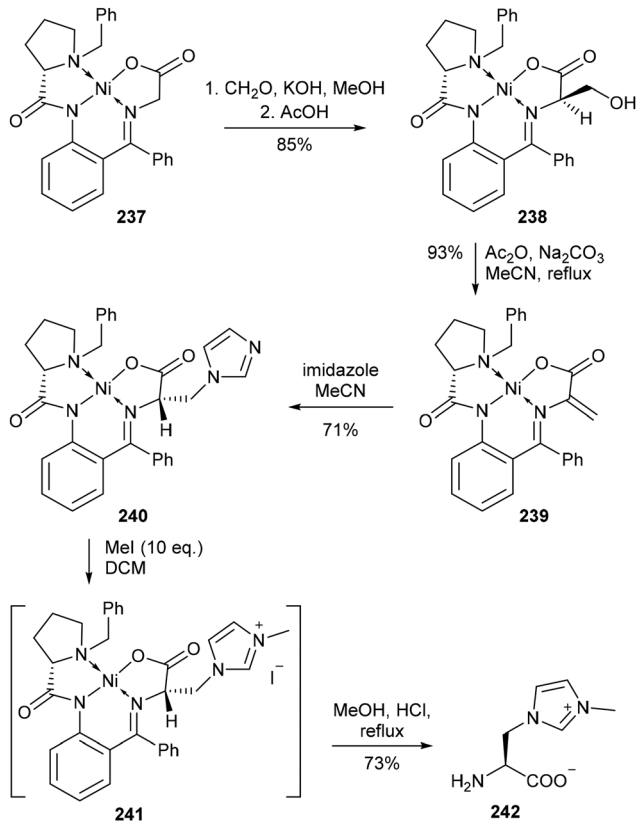


Fig. 4 Metal complexes of peptides with NHC-containing amino acids derived from aspartic (n = 1) or glutamic acid (n = 2) and thiazolylalanine **236**.

tide **233** effectively complexed to rhodium following transmetallation of the corresponding Ag(I) complexes.

In 2020, Metzler-Nolte and co-workers expanded upon the toolbox for peptidic metal–NHC complexes (Fig. 4) including rhodium and iridium complexes using derivatives of aspartic acid (n = 1) and glutamic acid (n = 2),[140] as well as thiazolylalanine, with which ruthenium complex **236** was prepared.[141] These imidazolium-functionalised amino acids were incorporated into peptides *via* SPPS and successfully transformed into metal–NHC complexes using a standard transmetallation protocol, giving metallopeptide complexes of the type shown in Fig. 4.

In 2008, Belokon and co-workers reported the synthesis of **242**, a novel imidazolyl amino acid with unique connectivity, wherein the amino acid functionality is attached *via* an imidazole nitrogen (Scheme 47).[142] This amino acid was accessed using an approach based on their seminal 1986 report in which the use of Ni(II) complexes of glycine and [*N*-(benzylprolyl)amino]benzophenone Schiff bases for enantioselective amino acid synthesis was first detailed.[143] Following the formation of **238** through base-catalysed condensation of Ni(II)–



Scheme 47 Synthesis of an imidazolyl amino acid using a chiral masked glycine Ni(II) complex – Belokon and co-workers.[142]

glycine complex **237** with formaldehyde, dehydration *via* acetic anhydride with catalytic sodium carbonate gave dehydroalanine complex **239**, furnished with a carbon–carbon double bond suitable for a Michael addition reaction with imidazole

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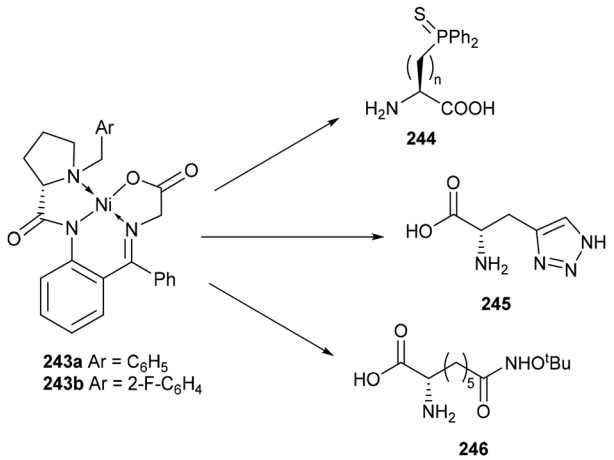
as a nucleophilic donor component.[144] From here, the resulting addition product **240** was treated with methyl iodide to give the corresponding ionic imidazolium complex **241**, from which the desired amino acid **242** was obtained by refluxing a methanolic solution of the Ni(II) complex with hydrochloric acid. Reaction of **242** with Boc_2O gave the *N*-Boc-protected amino acid, which was successfully converted into the corresponding silver complex using a routine procedure.[145] Shortly after, the same group expanded upon this method both by introducing a variety of substituted imidazole components at the Michael addition step and by varying the alkyl halide in the subsequent alkylation step, however, the coordination of these amino acids to metals was not investigated.[146]

Since the pioneering work of Belokon and co-workers, the use of Ni(II) complexes of amino acid Schiff bases has emerged as a prominent strategy for the asymmetric synthesis of structurally diverse unnatural α-amino acids, including but not limited to sterically strained,[147a,b] cyclic,[148a,b] fluorinated,[149a,b] fullerene-derivatised,[150] spin-labelled,[151] and isotopically labelled examples.[152a,b] Moreover, this methodology has seen significant expansion in scope over the past decade. While the original reports detailed transformation of the glycine moiety by aldol and Michael addition processes,[143,144] numerous other examples of reaction types have since been demonstrated, including alkyl halide alkylations, dialkylations, Mannich reactions,[153a–c] and more recently, Heck,[154] Suzuki,[155] reductive olefin coupling,[156] allylic alkylation,[157] cyclopropanation,[158] electrochemical thioalkylation[159] and radical perfluoroalkylation reactions.[160] In-depth discussions of this methodology can be found in the following reviews.[161a,b]

The use of nickel templating has also widely been applied to the synthesis of amino acids containing metal-binding groups. In 2009, Burck and co-workers utilised the prototypical Belekon template **243a**,[143] the Ni(II) Schiff base complex of (*S*)-2-[*N*-(benzylpropyl)-amino]benzophenone, to create a chiral environment allowing for enantioselective alkylation with a phosphine-containing reagent with varying lengths of alkyl linker (Scheme 48).[162] Installation of an Fmoc group into the sulphide-protected derivatives **244** enabled the authors to incorporate these amino acids into cyclic peptides based on the natural product Gramicidin S. Subsequently, Rh(I) and Pd (II) complexes based upon the bisphosphine-functionalised decapeptide were demonstrated to be catalytically active in asymmetric hydrogenation and allylic substitution reactions, showing moderate ee of up to 52% in the hydrogenation of dehydroalanine.[163] More recently, Belokon and co-workers reported an efficient synthesis of 1,4-substituted 1,2,3-triazole containing amino acid **245** by combining their Ni(II) template approach with the well-established copper(I)-catalysed azide alkyne cycloaddition (CuAAC) click reaction.[164] Following derivatisation with an alkyne side chain, the prototypical Ni(II)–glycine complex **243a** was mixed with an alkyl azide and catalytic copper iodide under basic conditions to give the corresponding triazole, which was then subjected to acidic hydrolysis to generate the desired amino acids in high yield (93–96%)



Scheme 48 Application of the Belekon template for the synthesis of amino acids containing metal-binding groups.

and ee (>99%).[165] Although their metal-coordinating behaviour was not explored by the authors, the chelating ability of triazole-functionalised amino acids and peptides is well-documented in the literature,[166a,b] particularly in the context of biomolecule radiolabelling for theranostics applications.[167a,b] In 2019, Jamieson and coworkers used a chiral Ni(II) Schiff base complex containing a fluorinated analogue of the original BPB chiral auxiliary (**243b**) in an alkylation reaction with 6-bromo-*N*-(*tert*-butoxy)hexanamide.[168] Subsequent decomplexation and installation of an Fmoc group afforded Fmoc–Asu(NHO^{t}Bu)–OH (**246**) which was used to construct peptides with zinc-binding hydroxamic acid sidechains for evaluation as HDAC inhibitors.

Aside from catalysis, *N*,*N*-functionalised NHC amino acids have been shown to hold potential in biomedical applications, particularly in the development of biocompatible gold nanoparticles (AuNPs). In 2017, Reithofer and co-workers first demonstrated the applicability of NHC ligands derived from *N*-Boc histidine methyl ester in the stabilisation of AuNPs with optical activity.[169] Given the importance of aqueous stability and solubility in the design of biocompatible nanoparticles, the group sought to modify their histidine-derived AuNP. By instead forming the Au(I) complex with *N*-acetyl protected L-histidine ethyl ester as a precursor, followed by *N*-alkylation and saponification of the ester, the authors were able to create a water-soluble and pH responsive variant of the NHC-stabilised AuNP.[170] These complexes were subsequently evaluated for their pharmacological properties, including toxicity and relative stability in human serum, using inductively coupled plasma mass spectrometry (ICP-MS) methodology.[171] In 2020, Kühn and co-workers reported the synthesis of a series of bis-NHC complexes derived from histidine through a benzylation and metal complexation sequence (Scheme 49).[172] Subsequent biological evaluation indicated a link between the nature of the wingtip substituent and the antiproliferative activity of the complex, wherein a greater lipophilicity led to greater potency against a selection of cancer cell lines. Notably, multiple com-

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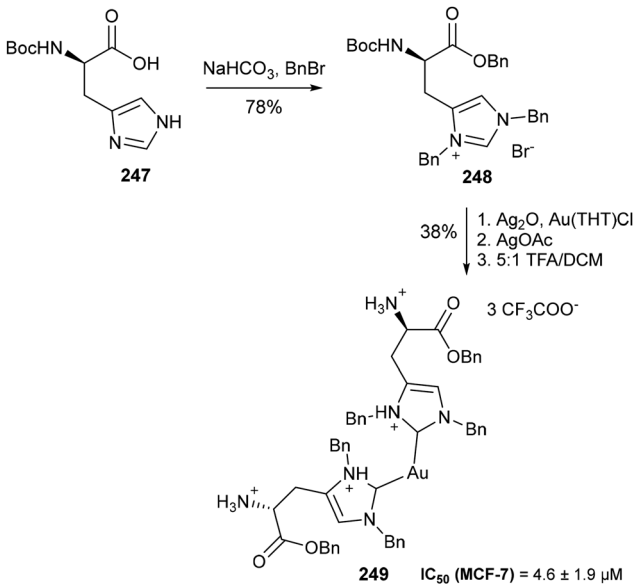


Scheme 49 Synthesis of a histidine-derived Au(I)-bis NHC complex with potent antiproliferative activity against the MCF7 cell line – Kühn and co-workers.[172]

plexes including **249** exhibited antiproliferative activity towards MCF7 (breast) cells significantly greater than the widely used metallodrug cisplatin (IC_{50} = 21 ± 6.3 μM) and comparable to that of auranofin (IC_{50} = 0.28 ± 6.3 μM).

4.2. Metallocene amino acids

The incorporation of cyclopentadienyl (Cp) rings into peptides has emerged as a promising strategy in the design of β-turn mimetics for the development of functional peptide β-sheet systems. This concept was first recognized in 1996 by Herrick and co-workers, who prepared mono- and bis-amino acid ferrocenyl complexes by reacting the methyl ester hydrochloride of the amino acid with 1,1′-ferrocene mono- or di-carbonyl chloride respectively.[173] Subsequent spectroscopic analysis showed lowering of N–H amide and C═O ester IR stretches for the bis- compared with the corresponding mono-complexes, as well as deshielding of the ^{13}C NMR resonance observed for the ester carbonyl carbon moving from the mono- to bis-complex, with the carbon of the corresponding amide group remaining virtually unaffected, pointing towards the formation of hydrogen bonding interactions between the NH proton and ester carbonyl, as depicted in Fig. 5.

Modification of the amino acid N-terminus with a metallocene fragment has been widely reported since the first example by Schlögl and co-workers in 1957 for use in peptide labelling and construction of beta turn mimics.[174] Fca (**254**) initially reported in 1998 by Butler and co-workers, represents the first example of a metallocene-containing unit containing both an available *N*- and *C*-terminus for peptide bond formation. Among a series of heterosubstituted aminoferrocenes, Fca was synthesized starting from 1,1′-dibromoferrocene **252** (Scheme 50A).[175] The corresponding bromo-1′-aminoferrocene

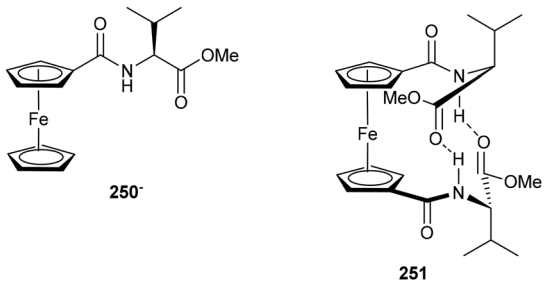
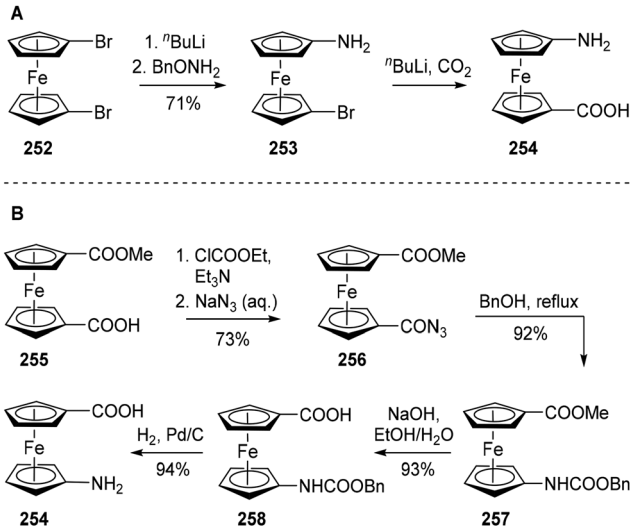


Fig. 5 Mono- (**250**) and bis- (**251**) valine ferrocenyl complexes – Herrick and co-workers.[173]



Scheme 50 Synthesis of 1′-aminoferrocene-1-carboxylic acid by (A) lithiation and carboxylation, and (B) Curtius rearrangement and hydrogenolysis.[175,176]

253 was obtained first by monolithiation with ^{n}BuLi, followed by reaction with 0.4 equivalents of *O*-benzylhydroxylamine. Following further addition of excess ^{n}BuLi, the reaction was quenched using solid carbon dioxide, which was accompanied by the immediate precipitation of the target amino acid **254**. In 2002, Kovac and co-workers proposed an alternative synthesis of Fca starting from the ferrocenyl acid–ester **255** (Scheme 50B). Installation of the azide group to give **256** enabled the formation of carbamate **257** *via* a Curtius rearrangement upon heating with benzyl alcohol, which was followed by alkaline hydrolysis of the methyl ester group to give the acid–carbamate **258**. Finally, hydrogenolysis was performed using palladium on carbon to transform the carbamate moiety into an amine group to give the desired amino acid **254**,[176] which was later used to construct medicinally-relevant β-lactam-containing ferrocenyl peptides exhibiting stabilisation *via* a novel cooperative three-hydrogen-bond network.[177] Metzler-Nolte and coworkers reported the first example of incorporating Boc-protected Fca **259** into an oligopeptide, demonstrating its compatibility with typical peptide

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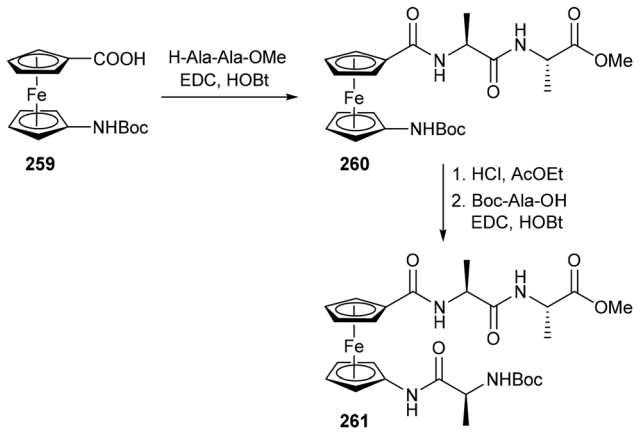
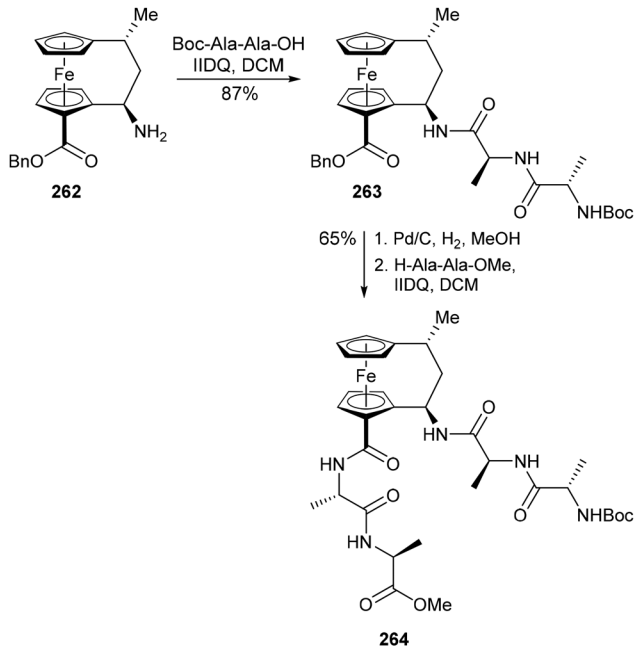
coupling conditions *via* both the *N*- and *C*-termini (Scheme 51).[178]

Since the synthesis of Fca (**254**) a range of structurally diverse amino acids containing the ferrocene moiety have emerged in the literature. The ferrocenophane amino acid **262** (Scheme 52) is an example where the amino and carboxyl groups are homoannularly substituted,[179] meaning these two functionalities are connected to the same Cp ring, in contrast to **Fca** described previously. Further examples of related amino acids include the carbocyclic **265** and alkyl-linked **266** derived from glutamic acid (Fig. 6) – both of which were prepared in *N*-protected forms and successfully incorporated into peptides *via* solid phase and solution phase methods respectively.[180a,b]



Scheme 51 Incorporation of **Fca** into a peptide *via* both C- and N-termini – Metzler-Nolte and co-workers.[178]



Scheme 52 Incorporation of a ferrocenophane amino acid into a peptide *via* both C- and N-termini – Erker and co-workers.[179]

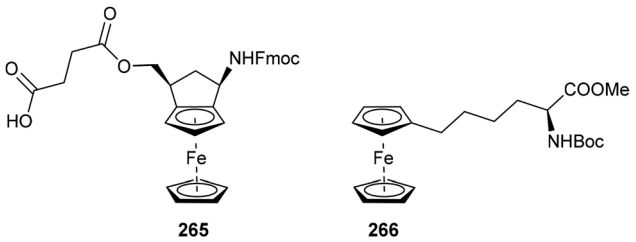
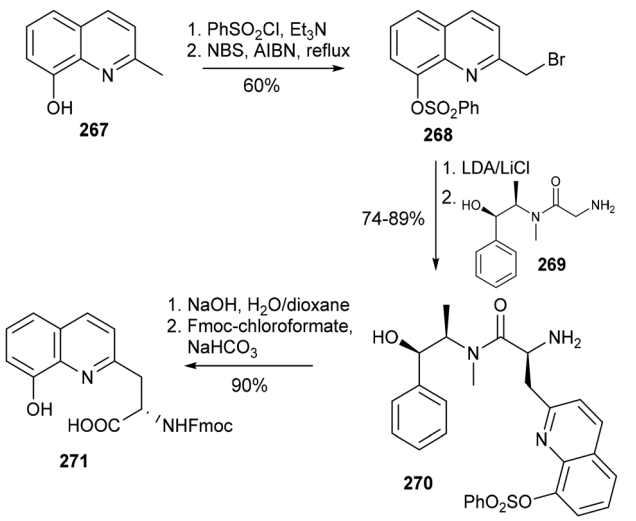


Fig. 6 Examples of structurally diverse ferrocenyl amino acids used for peptide synthesis.[180a,b]

5. Complex heterocyclic

Aside from the pyridyl- and extended pyridyl-systems described in section 3, numerous additional examples of heterocyclic ligands exist in the literature encompassing a mixture of coordinating heteroatoms and denticities. One notable example is 8-hydroxyquinoline, a medicinally-relevant scaffold comprised of a pyridine ring fused to benzene, with a single hydroxyl substituent at a particular location around the ring.[181] In the context of peptide chemistry, the first example of an amino acid synthesized with this functionality was reported by Imperiali and co-workers in 1998.[182] The 2-substituted amino acid **271** was synthesized with high diastereoselectivity starting from 8-hydroxy-2-methylquinoline **267**, using asymmetric alkylation methodology developed by Myers and co-workers involving pseudoephedrine glycinamide as a chiral auxiliary (Scheme 53).[183] To begin with, **267** was converted into the corresponding bromide **268** using radical bromination *via* the protected benzenesulfonate ester. The chiral auxiliary (**269**), prepared by the selective *N*-acylation of pseudoephedrine with the mixed anhydride of *N*-Boc–glycine, was then incorporated to introduce the desired L-configuration to the amino acid, which was subject to alkaline hydrolysis to ultimately give the



Scheme 53 Asymmetric synthesis of an amino acid containing the 8-hydroxyquinoline scaffold – Imperiali and co-workers.[182]

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Fmoc-protected derivative **271** for incorporation into a peptide. Additionally, a 5-substituted analogue was prepared *via* the same method shown in Scheme 53 using the 5-methyl starting material derivative – these two hydroxyquinoline-containing amino acids were subsequently used for the synthesis of short peptides that displayed significant selectivity for Zn(II) over a selection of other divalent metals, demonstrating potential for application in the design of a Zn(II) chemosensor.

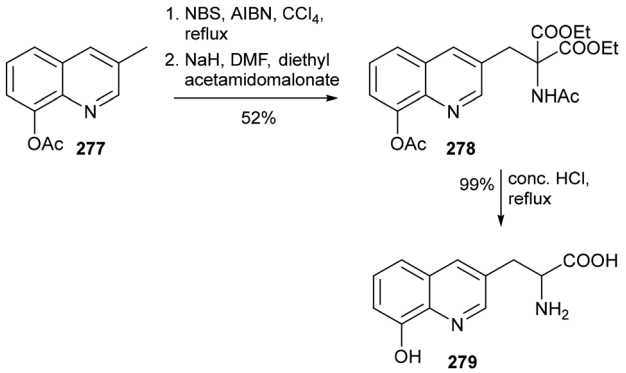
While **271** was found to show good selectivity for Zn(II), a residue with a longer excitation wavelength was desired to facilitate the construction of a sensitive fluorescent sensor capable of monitoring Zn(II) concentrations in real time. Imperiali and co-workers addressed this by synthesizing the phenyl-substituted derivative **276** *via* a Suzuki-type coupling of benzeneboronic acid to the brominated hydroxymethylquinoline **272**, followed by asymmetric alkylation with *N*-(diphenylmethylene)glycine *tert*-butyl ester in the presence of a phase transfer catalyst (Scheme 54).[184] As expected, extension of the conjugated system in the metal-binding residue induced a red shift of fluorescence emission absorption bands to 269 and 391 nm compared with 251 and 357 nm for an analogous peptide containing amino acid **271**.

Aside from the above examples, a racemic 3-substituted hydroxyquinoline alanine derivative (8HQ–3Ala) has been synthesized by Schultz and co-workers by radical bromination followed by formation and hydrolysis of a malonate (Scheme 55).[185] The amino acid (**279**) was then genetically encoded into *E. coli* and used for the incorporation of a Zn^{2+} binding site into *O*-acetylserine sulphydrylase.

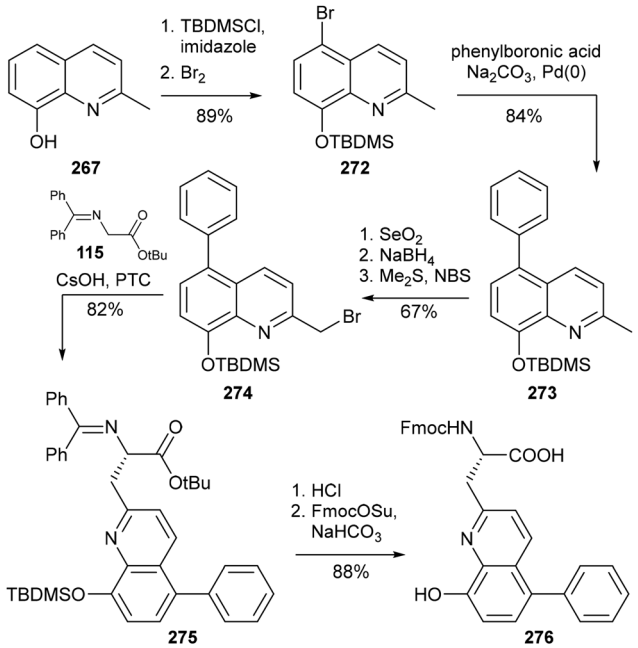
In 2022, Banwell and co-workers reported a stereodivergent route for accessing the enantiopure forms of the 3-substituted hydroxyquinoline amino acid.[186] Their approach centred around the rhodium-catalysed asymmetric hydrogenation of a dehydroamino acid precursor, a widely-precedented strategy in the literature used for obtaining enantiomerically enriched amino acids.[187] Using methodology reported by Meth-Cohn for the synthesis of quinolines,[188] acetanilide **280** was treated with DMF and phosphorus oxytrichloride to obtain the *O*-protected hydroxyquinoline scaffold **281** containing an aldehyde moiety. From here the required dehydroamino acid (**283**) was prepared *via* the azlactone method, where *N*-acetyl glycine cyclises and condenses with aldehyde **281** to give the oxazolone **282**, which is converted into **283** through ring opening with sodium acetate in methanol (Scheme 56). A rhodium(I) complex combined with a DuPHOS-type ligand was used to catalyse the hydrogenation of **283** into **284** with 98% ee, which was then subject to Pd-catalysed reductive dichlorination to give the *N*- and *C*-protected amino acid **285**. Although a successful deprotection procedure, treatment of **285** with aqueous HBr led to trace impurities arising from unwanted electrophilic bromination of the phenolic ring, therefore purification was carried out by preparative reversed-phase HPLC to obtain **286** as a bis-TFA salt in 44% yield.

Benzoxazole – a heterocyclic aromatic system containing a five-membered oxazole fused to a phenyl ring – represents another important scaffold on account of its diverse bioactivity and propensity towards complexation with a wide range of metals.[189] Numerous examples of amino acids containing this moiety have been reported in the literature, following the first synthesis of a benzoxazol-5-yl alanine derivative reported by Guzow and co-workers involving the catalytic reduction of 3-nitro-L-tyrosine **287**, formation of a Schiff base (**288**) and cyclisation into benzoxazole **289** in the presence of lead tetraacetate as an oxidising agent (Scheme 57).[190]

This general approach based on the oxidative cyclisation of a Schiff base formed from the reaction of a tyrosine derivative with various aldehydes has been utilised in the design of fluorescent metal sensors. Examples of metal-binding moieties that have been incorporated into benzoxazole amino acids include quinoxaline,[191] thiophene,[192] and imidazole,[193] as highlighted in Fig. 7.



Scheme 55 Racemic synthesis of a 3-substituted amino acid containing the 8-hydroxyquinoline scaffold – Schultz and co-workers.[185]



Scheme 54 Synthesis of a hydroxyquinoline-containing amino acid with a phenyl substituent – Imperiali and co-workers.[184]

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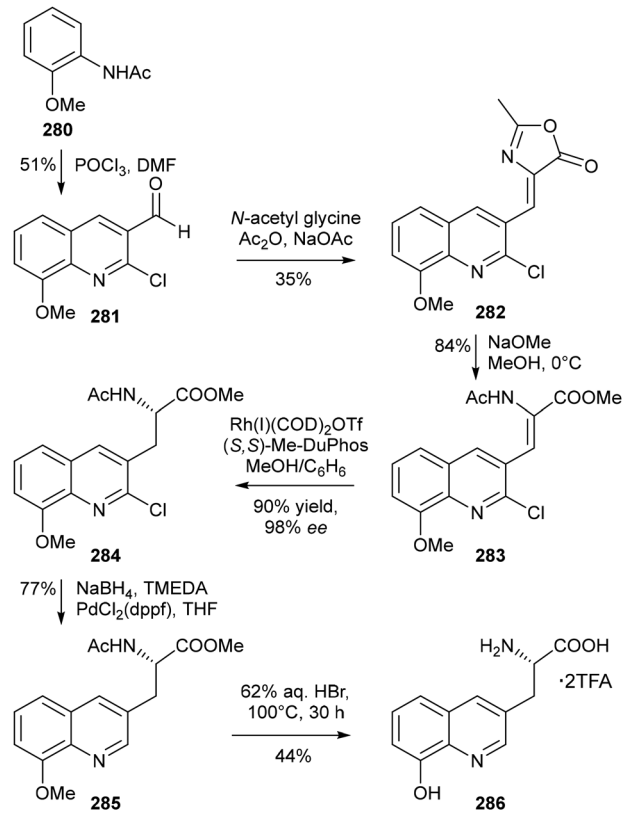
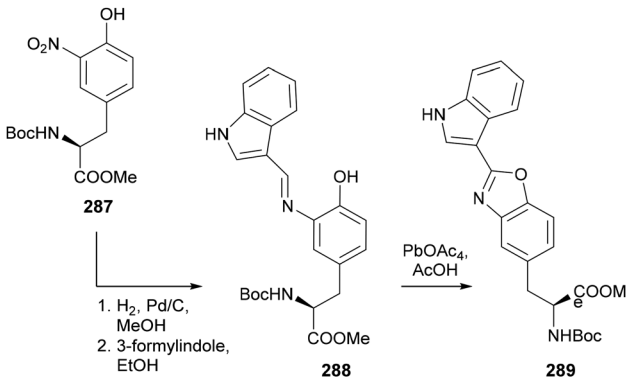


Scheme 56 Asymmetric synthesis of 8HQ–3Ala *via* Rh-catalysed hydrogenation of a dehydroamino acid precursor – Banwell and co-workers.[186]



Scheme 57 Synthesis of a benzoxazol-5-yl alanine derivative – Guzow and co-workers.[190]

In 2011, Costa and co-workers reported the design of a series of peptidic metal-ion sensors featuring a benzoxazole chromophore with high sensitivity towards Hg^{2+} ions.[194] The peptide **293** (Fig. 8), synthesized by carbodiimide-mediated coupling of thiophene benzoxazole amino acid **291** to a protected Cys–Ala dipeptide, was able to detect both Hg^{2+} and Ag^{+} ions in water when inserted into silica core/PEG shell nanoparticles, demonstrating the potential of such nanoarchitectures as sensitive metal ion sensors in a biological setting.

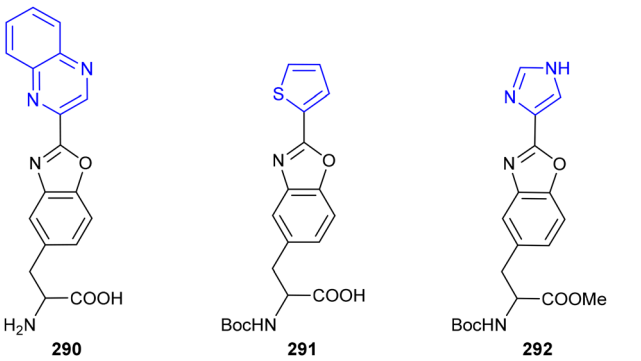


Fig. 7 Examples of amino acids containing benzoxazoles functionalised with various metal-binding groups (shown in blue).

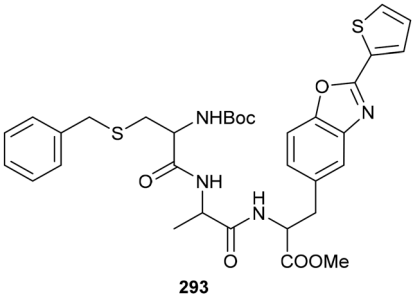


Fig. 8 A benzoxazole-containing fluorescent peptide for the sensing of metal ions – Costa and co-workers.[194]

An assortment of other unnatural amino acids containing diverse metal-binding heterocycles has been generated from protected 4-formyl phenylalanine **294** as a starting material. Selected examples, summarised in Scheme 58, include the pyridyl-containing trriarylimidazole amino acid **296**,[195] benzimidazole derivative **298**,[196] and hydrazone-containing one **300**.[197]

6. Macrocyclic

Cyclen is a nitrogen-containing macrocycle known for its strong, multi-dentate, coordinating abilities towards a broad range of metal ions, including both transition metals and lanthanides. In 2003, Suh and co-workers reported the Cu^{2+}- and Co^{2+}-binding cyclen-functionalised lysine derivative **302**, prepared by the attachment of a Boc-protected cyclen moiety to the ε-amino group of *N*-acetylated lysine (Fig. 9).[198] In a similar fashion, König and co-workers synthesized a glutamic acid derivative functionalised with a cyclen group *via* the side-chain carboxylic acid group – the resulting amino acid was further modified with an Fmoc group to facilitate subsequent peptide coupling.[199]

The homoserine analog **306**, reported by Yu and co-workers, was prepared by first converting the hydroxyl group of *N*- and *C*-protected homoserine into the corresponding

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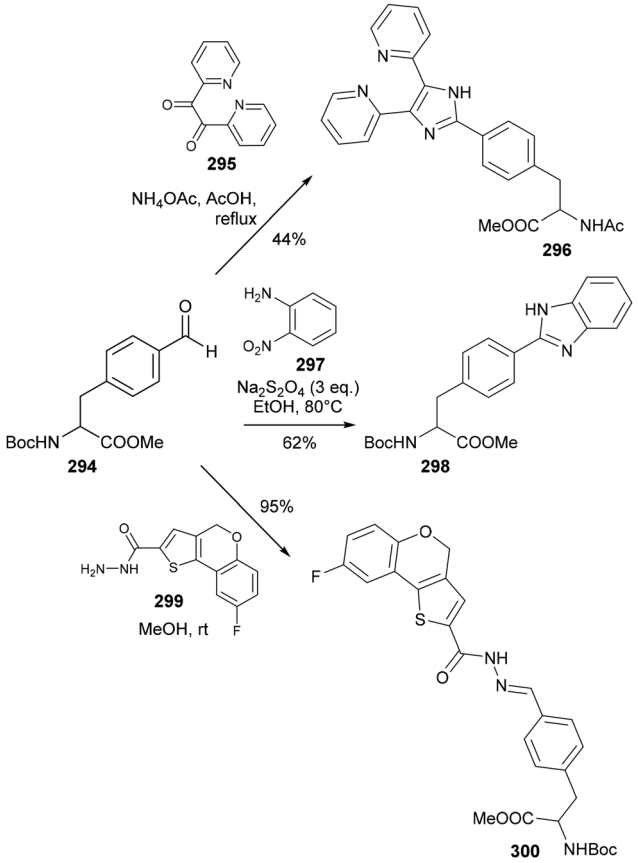


Scheme 58 Synthesis of various amino acids with metal sensing properties starting from an aldehyde-functionalised phenylalanine derivative – Costa and co-workers.[195–197]

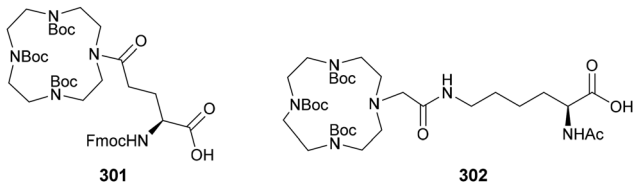
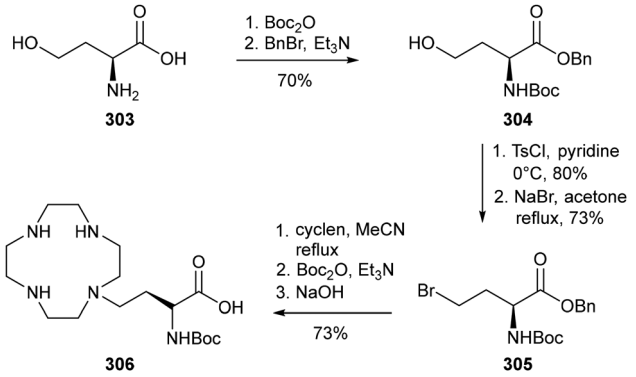
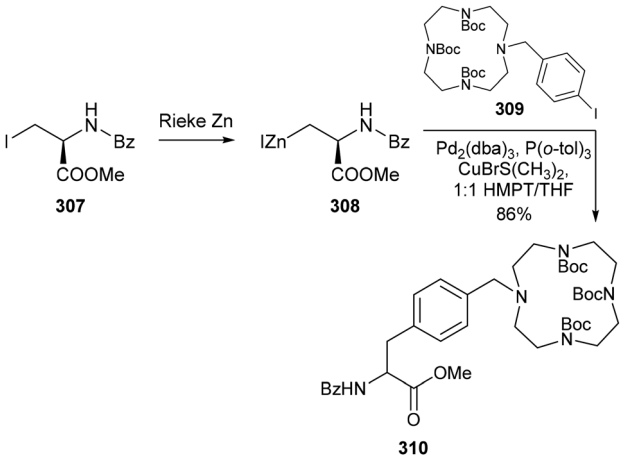


Fig. 9 Cyclen-functionalised derivatives of lysine (**302** – Suh and co-workers)[198] and glutamic acid (**301** – König and co-workers).[199]

bromide **305** *via* the activated tosylated, followed by alkylation with cyclen under reflux and *N*-Boc protection of the cyclen amines (Scheme 59). Alkaline hydrolysis afforded the desired amino acid **306**, which was successfully coupled to L-alanine methyl ester using DCC and HOBt to give the dipeptide in 75% yield.[200] In 2006, König and co-workers reported the first application of a Negishi coupling using *p*-iodoaniline derivatives (Scheme 60).[201] Among the several examples of phenylalanine derivatives was the synthesis of cyclen-functionalised **310**, where the aryl iodide partner **309** was produced by reacting 1-bromomethyl-4-iodobenzene with cyclen under basic conditions.



Scheme 59 Functionalisation of the L-homoserine sidechain with cyclen – Yu and co-workers.[200]



Scheme 60 Synthesis of a phenylalanine derivative containing a cyclen moiety in the sidechain by Negishi coupling – König and co-workers.[201]

In 2007, König and co-workers reported the synthesis and incorporation of the bis-cyclen amino acid **312** into a polyalanine peptide (Scheme 61).[120] The triazine-bis-cyclen structure **311** was prepared from Boc-protected cyclen and trichlorotriazine as previously reported,[202] to which a lysine unit was appended *via* a nucleophilic aromatic substitution reaction to form the target Fmoc-protected amino acid **312**. By using the coupling agents HOAt and HATU with collidine as a base, **312** was successfully coupled to alanine residues at both termini, giving rise to peptide **313** capable of binding two Zn^{2+} ions *via* the cyclen moieties.

A closely related aza-crown ether, triazacyclononane (tacn), has also been used in the synthesis of metal-binding peptides. The first example of a tacn-functionalised amino acid was reported by Scrimin and co-workers in 1999, wherein the *N*-Cbz protected amino acid **316** was obtained by the reaction of the doubly protected triazacyclononane **314** with the β-lactone form of L-serine (**315**) in 80% yield (Scheme 62).[203] When incorporated twice into a helix-forming heptapeptide, this residue enabled the formation of a dinuclear zinc complex

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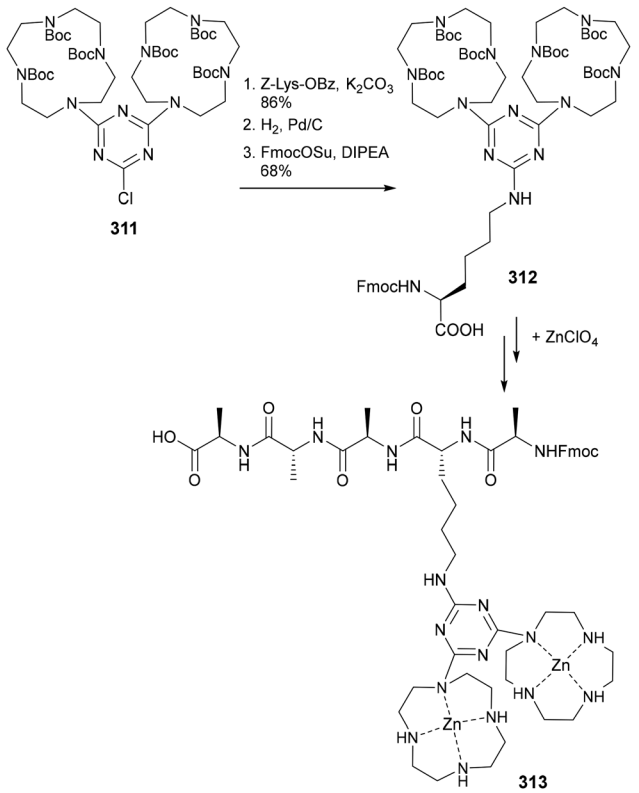
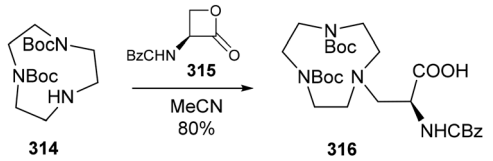


Scheme 61 Preparation of a peptide containing a bis-Zn^{2+}-bis-cyclen functionality – König and co-workers.[120]

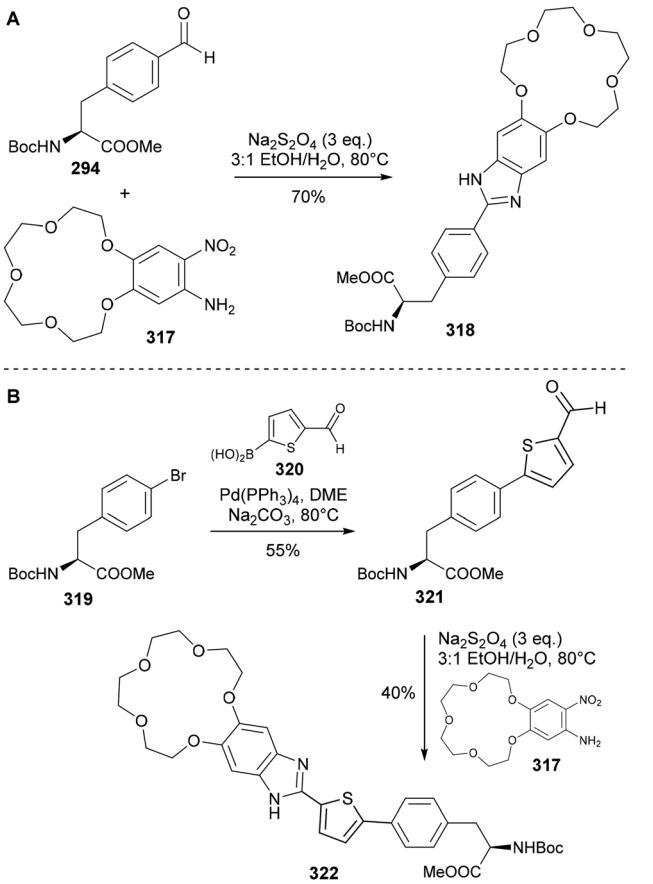


Scheme 62 Preparation of a triazacyclononane amino acid – Scrimin and co-workers.[203]

that showed catalytic activity both in the intramolecular transesterification of a RNA model substrate and in the hydrolysis of plasmid DNA,[204a,b] with cooperativity observed between the two metal ions. The same group has also reported the design of an artificial metallonuclease with a well-defined helix-loop-helix tertiary structure, where the extent of helical content was dependent on the coordination of four units of the amino acid **316** to zinc ions.[205]

The crown ether is a unique heterocyclic scaffold typically characterised by repeating ether linkages, although substitution of one or more oxygen atoms with other heteroatoms, typically nitrogen and/or sulphur, are well documented. Given their flexible macrocyclic nature, crown ethers are able to interact with a wide range of metal ions with high affinity on account of the chelate effect. Additionally, the tunability of the crown ether cavity size allows for highly specific binding of variously-sized metal cations, *e.g.* 18-crown-6 has a particularly high affinity for K^+, while 15-crown-5 accommodates the smaller Na^+ ion. These properties make the crown ether particularly suitable for the design of artificial receptors and chelation-based chemosensors.[206] In the area of peptide chemistry, the incorporation of crown ethers has been explored in the design of artificial membrane ion channels,[207a,b] as well as a means of constructing antimicrobial peptides with cell permeabilising properties.[208]

In addition to the examples shown in Scheme 58, the aldehyde-functionalised phenylalanine **294** has also been used as a precursor for the preparation of amino acids containing a crown ether moiety. In 2016, Costa and co-workers reported the synthesis of a phenylalanine derivative furnished with a 15-crown-5 macrocycle by the reaction of the aldehyde **294** and the 4-amino-5-nitro aryl crown ether species **317** in the presence of excess sodium thiosulphate (Scheme 63A).[209] To further tune the electronic properties of the amino acid, the authors designed further analogues incorporating a thiophene spacer unit. This was achieved first *via* the Suzuki coupling of *para*-brominated phenylalanine **319** and the boronic acid of 5-formylthiophene (**320**) to form aldehyde **321**, before the



Scheme 63 Synthesis of crown ether phenylalanine derivatives starting from (A) 4-formyl phenylalanine, and (B) a thiophene-containing phenylalanine derivative formed *via* Suzuki cross-coupling – Costa and co-workers.[209]

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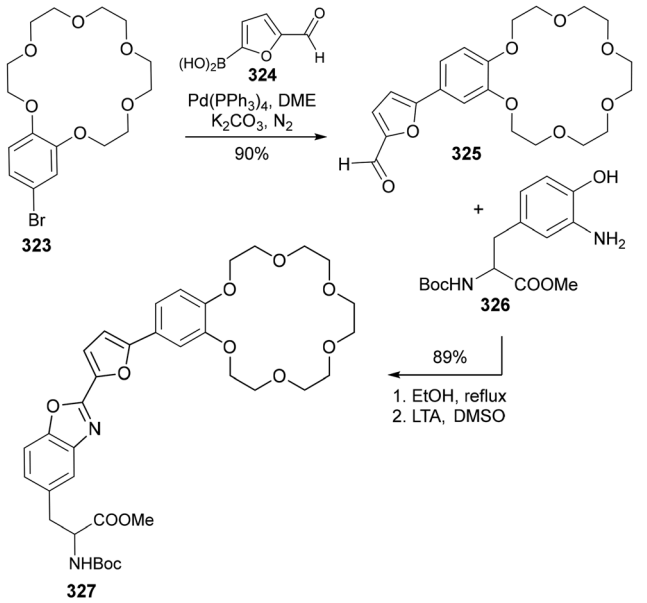
addition of the crown ether reagent **317** as seen in Scheme 63B.

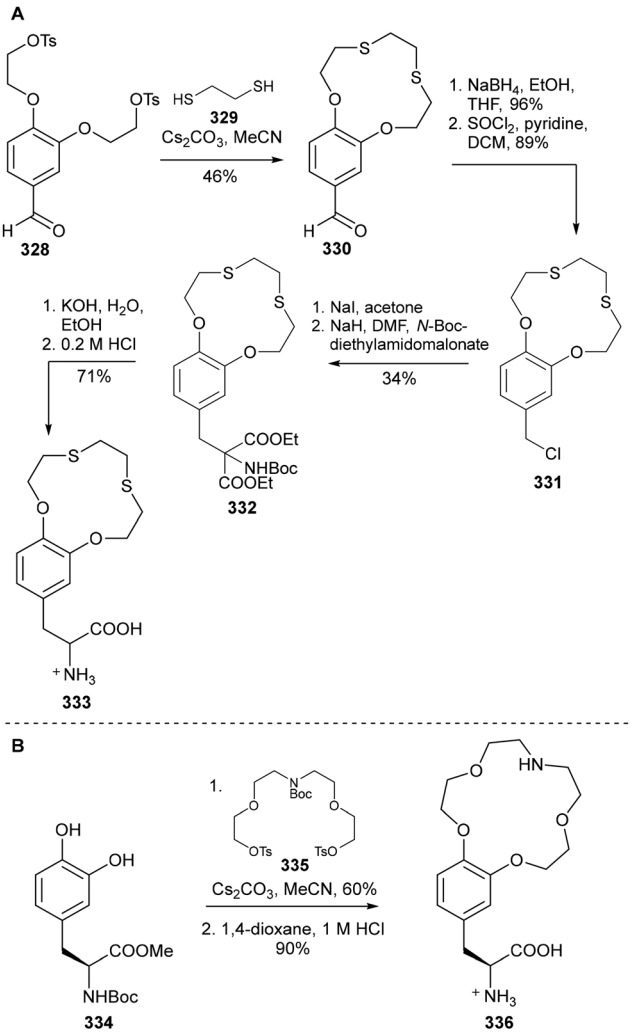
In 2023, the same group reported a new series of structurally diverse amino acids for use as fluorometric sensors of metal ions, applying similar methodology as previously described. Comprising a phenylalanine core, each of these analogues was functionalised with a benzoxazole reporting unit, a phenyl or heterocyclic π spacer, and a crown ether moiety of varying size.[210] To synthesize **327**, a representative example, the benzocrown bromide **323** was first coupled to 5-formyl-2-furanylboronic acid **320** in the presence of catalytic palladium to form the to form the corresponding aldehyde **321**, which subsequently underwent oxidative cyclisation with phenylalanine derivative **326** to form the required benzoxazole moiety (Scheme 64).

With the aim of expanding the scope of these amino acids beyond the archetypal crown ether, Budisa and co-workers have detailed two synthetic routes enabling access to amino acids with sulphur- and nitrogen-containing crown macrocycles (Scheme 65).[211]

The first of these methods is based upon the installation of a thiol nucleophile (**329**) to form a thiacrown from the tosylated precursor **328**, followed by conversion of the aldehyde into an amino acid moiety by introduction and alkaline hydrolysis of a diethylamidomalonate group. The second approach, using the linear nitrogen-containing crown ether precursor **335**, involved cyclisation of a DOPA analog **334** by nucleophilic displacement of the tosylated groups in **335**. Although their metal-binding properties were not investigated, the authors proposed that broadening the scope of available crown ether-based residues should give rise to amino acids with altered ion selectivity, allowing for the construction of more complex metal-sensing peptide architectures.



Scheme 64 Synthesis of a benzocrown ether amino acid featuring a furan spacer unit – Costa and co-workers.[210]



Scheme 65 (A) Synthesis of thia-crown amino acids, and (B) Synthesis of aza-crown amino acids - Budisa and co-workers.[211]

A prominent agent in the area of theranostics, DOTA is a macrocyclic ligand comprising up to four nitrogen atoms and four carboxylic acid groups capable of chelating a range of metals, particularly lanthanides. As a chelator, it is widely used in the form of a bioconjugate, typically either to enhance the effects of yttrium and lutetium radiotherapy in cancer patients, or to act as a Gd(III) MRI contrast agent.[212] Incorporation of DOTA into a peptide sequence is typically achieved through direct modification of the peptide either *via* the N-terminus, or *via* a lysine or tyrosine sidechain.[213] To increase the versatility of the available methodology, Sherry and co-workers reported the design of DOTA-containing amino acids compatible with standard SPPS conditions, such that the chelating moiety could be incorporated anywhere along a peptide sequence.[214] Specifically, this involved the incorporation of a DOTA derivative triply protected with acid-labile protecting groups into the amino acid sidechain, and installation of a Fmoc group onto the α-amino terminus. The phenylalanine derivative **342** was prepared starting from *para*-nitro

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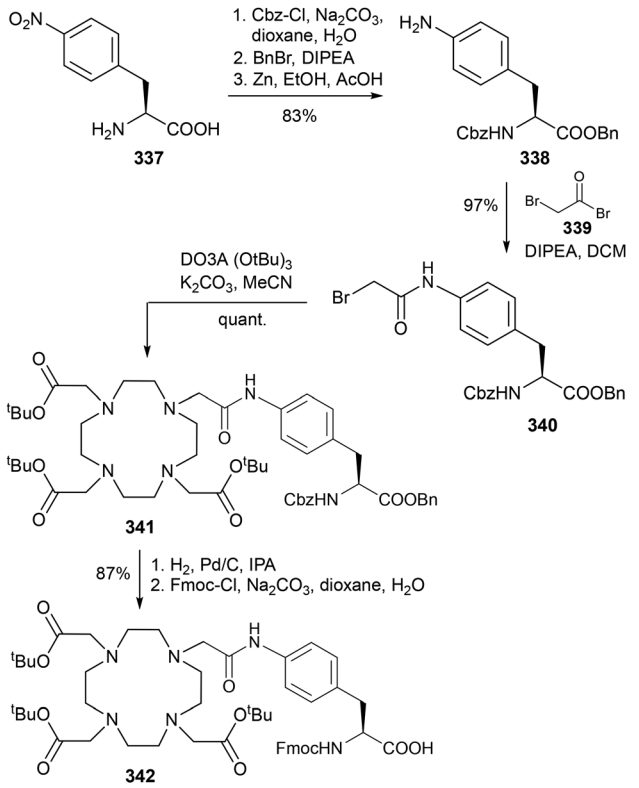
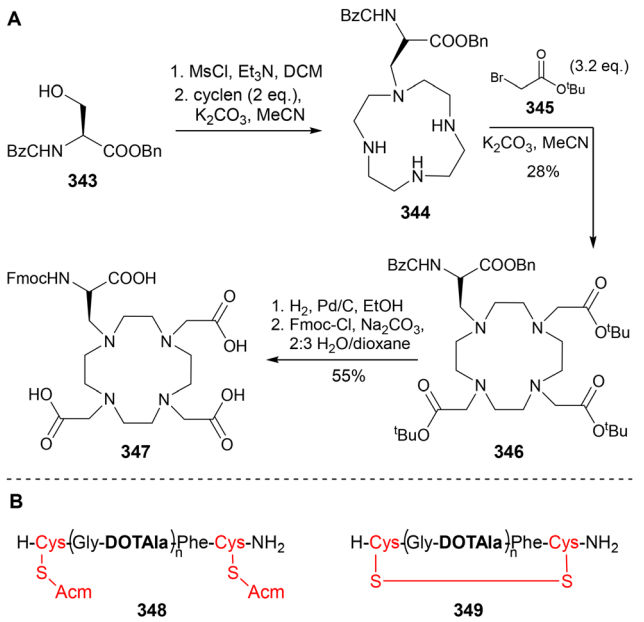
phenylalanine (**337**) which was furnished with Cbz and Bn protecting groups before reduction of the nitro group to give amine **338** (Scheme 66). From here the bromoacetylated intermediate **340** was formed, which was coupled to the free amine of the DO3A tris-*t*Bu ester to give **341**. Compound **341** was then transformed into the desired Fmoc-protected amino acid **342** following removal of the Cbz and Bn groups *via* catalytic hydrogenation. An analogous strategy was utilised to obtain a DOTA–lysine derivative, where the DOTA moiety was introduced through bromoacetylation of the ε-amino group. The utility of **342** as a building block for SPPS was demonstrated through the preparation of three model pentapeptides using HBTU activation chemistry, where deprotection of the DOTA esters was achieved using trifluoroacetic acid, in tandem with the resin cleavage step. Complexation with Gd^{3+} was carried out after purification of the crude DOTA-containing peptides, and the association constants of the resulting Gd^{3+}–peptide complexes confirmed *via* fluorescence polarisation, using a competitive binding experiment with an equivalent fluorescin-labelled peptide.

In 2012, a DOTA–alanine derivative **347** (DOTAla) was reported by Caravan and co-workers for the development of high relaxivity gadolinium-based MRI contrast agents.[215] Applying similar methodology to that of Sherry and co-workers, initial attempts to introduce the protected serine derivative **343** onto the *t*-butyl DO3A ester were unsuccessful. Therefore, a modified approach was taken wherein **343** was used to monoalkylate cyclen to give compound **344**, which was converted into the protected DOTA–alanine **346** upon further *N*-alkylation of the remaining cyclen amine groups using excess *t*-butyl bromoacetate (Scheme 67A). Following isolation of **346** *via* preparative HPLC, the target Fmoc-protected amino acid was obtained using standard procedures of hydrogenation and Fmoc installation, giving **347** in an overall yield of 15% over five synthetic steps. This amino acid (**347**) was subsequently used in the construction of a diverse peptide library, including sequences with up to three DOTAla units, in each case flanked by two cysteine residues (Scheme 67B). The cysteine residues were either left with Acm protecting groups intact, or deprotected to induce intramolecular cyclisation, demonstrating scope for the modification of peptide secondary structure. The corresponding Gd chelates were found to possess high thermodynamic stability and kinetic inertness, demonstrating the potential of these peptide frameworks in the design of new contrast agents.

A DOTA–lysine was reported by Linscheid and co-workers in 2014 for the construction of metalated peptides in the design of reporter probes for an ICP-MS-based DNA quantification assay.[216] Unlike the synthesis described by Sherry, **351** was synthesized by treating Fmoc–lysine with the *N*-hydroxysuccinimide ester of DOTA (**350**) in a TEAB buffer system, followed by complexation to either Tb^{3+} or Lu^{3+} (Scheme 68). By preparing the amino acid as a metal complex prior to use in SPPS, this approach allowed for the site-specific introduction of different lanthanides within one peptide sequence.



Scheme 66 Synthesis of a DOTA phenylalanine derivative for Fmoc peptide synthesis – Sherry and co-workers.[214]



Scheme 67 (A) Synthesis of DOTAla **X** and (B) peptide sequences assembled by Fmoc SPPS incorporating up to 3 repeating DOTAla residues – Caravan and co-workers.[215]

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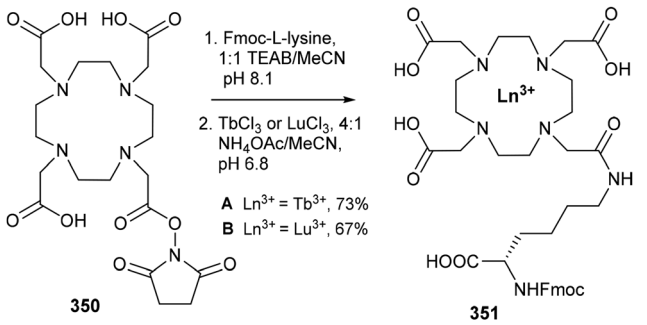

Scheme 68 Synthesis of a lysine–DOTA derivative complexed to a lanthanide metal ion – Linscheid and co-workers.[216]

7. Linear polydentate

The propensity of metal ions to stabilise the structural elements of synthetic peptides was first explored by the pioneering work of Ruan and co-workers, who observed that the helical content of peptides containing unnatural chelating residues could be drastically increased upon the addition of a divalent metal ion.[217] Bearing close resemblance to the classic chelator EDTA, aminodiacetic acid (Ada) **352** was chosen as a starting point for the design of the chelating amino acids **353** containing a $(CH_2)_nN$–$(CH_2COOH)_2$– sidechain (Fig. 10).

This design concept was built upon further by Schneider and co-workers in 2006, who reported a library of penta- and hexadentate chelating amino acids with sidechains based upon the aminodiacetic acid motif (Fig. 11).[218]

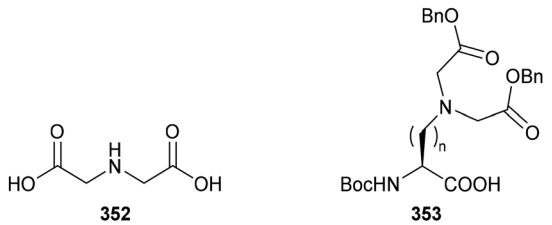

Fig. 10 Amino acids containing a chelating sidechain based on aminodiacetic acid **349**.[217]

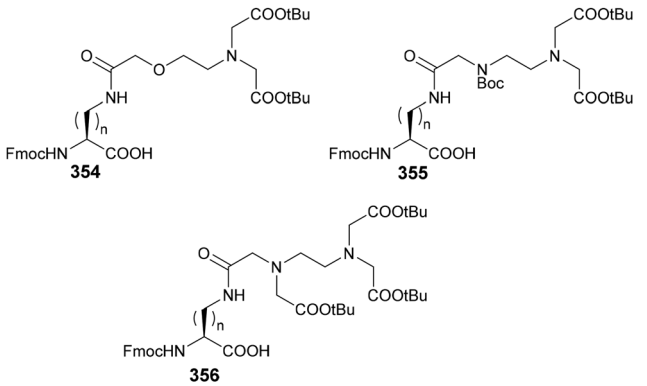

Fig. 11 Amino acids containing polydentate chelating sidechains – Schneider and co-workers.[218]

8. Conclusions

There are a wide variety of synthetic strategies to access metal-binding amino acids. This review has demonstrated that synthetic organic chemists have been able to access motifs which are not available to nature and successfully incorporate this into building blocks for peptide chemistry. The flexibility of synthetic approaches means that libraries of building blocks can be readily accessed which would not be practical through biosynthetic approaches, perchance. The chemistry outlined here demonstrates a straightforward way to diversify the functional groups and connectivity within amino acid architectures allowing for researchers to fully explore chemical space. This has been clearly demonstrated in the range of applications that these synthetic amino acids have been so far used in.

There are clear pathways to future impact using these strategies with innovative, sustainable approaches to catalysis being one. The chemistry detailed here is complementary to the work conducted by others, in fields such as directed evolution to allow metalloenzymes to conduct unnatural reactions under green reaction conditions. The use of synthetic amino acids should be further exploited to achieve similar goals. In addition, the strategies outlined here are synergistic with biological approaches for genetic incorporation of unnatural residues into proteins (*e.g.* stop codon suppression) where reliable synthetic routes to unnatural amino acids are a prerequisite for these processes. Therefore, to expand the toolbox of unnatural metal binding residues further exploration into synthetic methodology should be conducted.

Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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