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Negishi cross-couplings in the synthesis of amino acids

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The Negishi cross-coupling is a powerful C–C bond-forming reaction widely utilised in many areas of organic synthesis. This review details the use of Negishi cross-couplings in the synthesis of unnatural amino acids. The application of this reaction in the preparation of aromatic, heteroaromatic, and, complex amino acid derivatives are reviewed and presented herein.

Introduction

Negishi cross-coupling, since its original development in 1977 by Negishi and co-workers, has become a widely-utilised reaction in the field of organic chemistry.[1] Employing either palladium or nickel as a transition metal catalyst, the Negishi cross-coupling will form a new carbon–carbon bond between an organic halide/triflate and an organozinc reagent.[2,3] As a versatile route to form carbon–carbon bonds the Negishi cross-coupling has seen widespread use in the synthesis of many novel structural motifs.[4–6] In recent years, developments in Negishi cross-couplings by researchers, such as Fu, has allowed the transformation to be applied to more substrates than ever before.[7–10]

One application of the Negishi cross-coupling reaction is in the synthesis of unnatural amino acids. The formation of such compounds is of interest to a multitude of chemical and biological research arenas. Introduction of unnatural amino acids into peptide sequences has been used to probe protein structure and function in both *in vitro*[11,12] and *in vivo* systems.[13,14] Antibiotic peptides have utilized unnatural amino acids to increase organism selectivity, potency and metabolic stability.[15]

In recent years asymmetric catalysis has employed unnatural amino acids as easily accessible chiral building blocks for the synthesis of new ligands.[16–20] For example, chiral ligands such as PyBOX and BOX rely on the chirality afforded by natural or unnatural amino acids in their preparation and design.[21–24]

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William D. G. Brittain obtained an Msci degree from the University of Birmingham in 2013. He then went on to carry out PhD studies at the same institution on asymmetric copper catalysis under the supervision of Dr John S. Fossey (University of Birmingham) and Dr Benjamin R. Buckley (Loughborough University). During 2015/16 he spent time working with Professor Eric V. Anslyn (University of Texas at Austin) on boronic acid based assemblies. He is currently a post-doctoral research associate at Durham University in the Cobb group, where he is working in the areas of organic synthesis and peptide chemistry.

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With wide-ranging applications, methods to form unnatural amino acids are without doubt important. This review gives an overview and update[25] of the synthesis and derivatisation of amino acids through Negishi cross-couplings. Three major classes of derivatisation are discussed: aromatic-, heteroaromatic and more complex unnatural amino acids. Several mechanistic studies have been carried out on the Negishi cross-coupling of alkylamido zinc reagents, and these are also discussed.

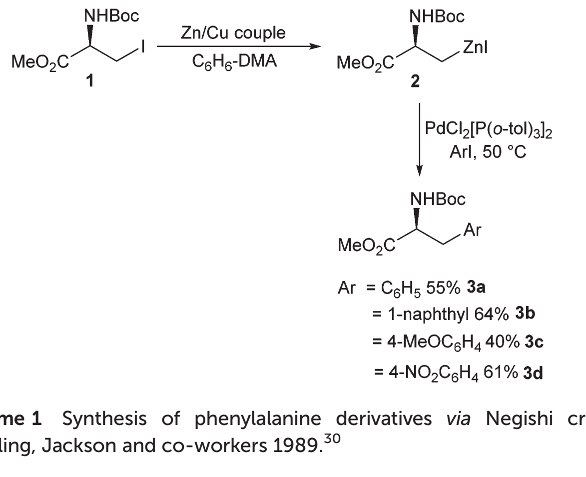
Synthesis of aromatic amino acids

Aromatic amino acids have been shown to have a broad range of utility. Aromatic amino acids have been successfully employed in natural product synthesis,[26] peptide chemistry[27,28] and drug development.[29] Therefore, facile synthesis of aromatic amino acids is important.

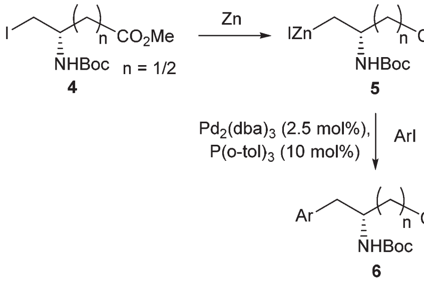
The area of Negishi cross-coupling to form stereo-defined aromatic amino acids was pioneered in the seminal work by Jackson *et al.* in 1989.[30] A range of novel single-enantiomer substituted phenylalanines **3a–d** were reported from the cross-coupling between an iodozinc L-serine derivative **2** and a range of *para*-substituted iodobenzenes (Scheme 1). The transformation was found to be tolerant to Boc protecting groups and a range of electron-donating (Scheme 1, **3c**) and withdrawing groups (Scheme 1, **3d**) on the aryl iodide component. The novel phenylalanine derivatives were isolated in yields of between 35% and 65%.

Jackson and Dexter would adapt their initial Negishi cross-coupling methods to also produce β and γ amino acids from aspartic and glutamic acid derivatives.[31] Utilising activated zinc and $Pd_2(dba)_3$, a range of β and γ amino acids were furnished in yields between 33% and 89% (Scheme 2). The scope and reproducibility using this methodology was found to be superior to the conditions initially used to access α amino acids.[30]

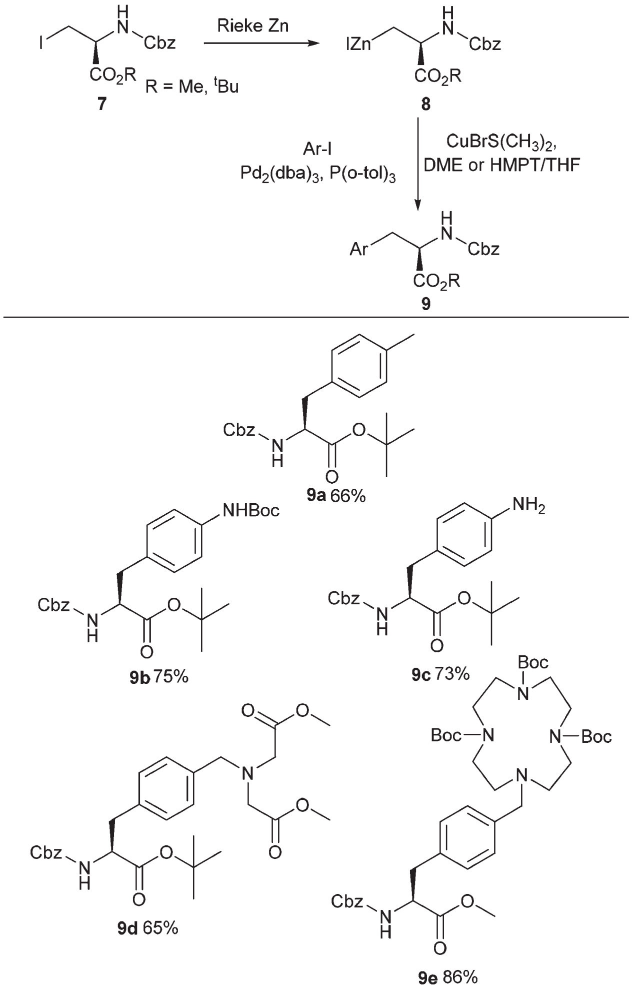
Modification of serine and phenylalanine *via* Negishi cross-coupling was reported by König and co-workers (Scheme 3).[32] Using Rieke zinc they were able to successfully form organozinc species from amino acids, which could then be coupled with electron-rich iodoanilines and iodobenzyl amines. Using this approach, a series of metal-chelating side chain containing unnatural amino acids **9a–e** were successfully synthesised in yields ranging between 65% and 86% (Scheme 3).



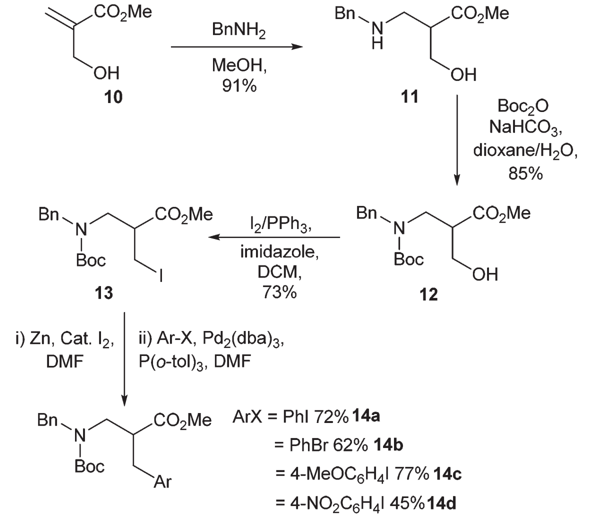
Scheme 1 Synthesis of phenylalanine derivatives *via* Negishi cross coupling, Jackson and co-workers 1989.[30]



Scheme 2 Synthesis of aspartic and glutamic acid derivatives utilising Negishi coupling, Jackson and Dexter, 1998.[31]



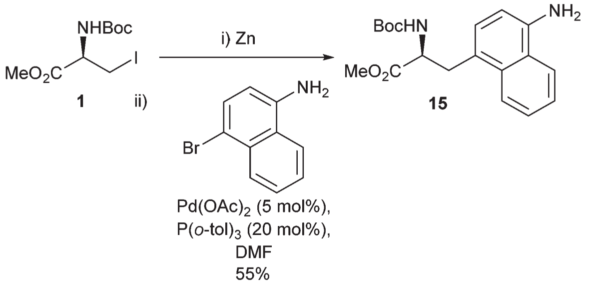
Scheme 3 Synthesis of novel amino acids containing metal-coordinating side chains, König and co-workers.[32]



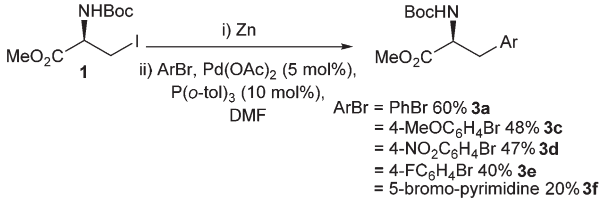
Scheme 4 β^2-Amino acids synthesised through Negishi cross couplings, Jackson and co-workers.[33]

The synthesis of β^2-homophenylalanine derivatives using Negishi cross-couplings were first reported in 2008 (Scheme 4).[33] The synthesis of the corresponding β^3-amino acids had already been reported in 1999,[34,35] but the methodology had not been used to access β^2-amino acids. Conjugate addition of benzylamine to compound **10**, followed by Boc protection and alkyl iodide formation, led to the protected amino acid coupling partner **13** (Scheme 4). Cross-coupling was then achieved using a range of aryl iodides and bromides. In the case of nitro-substituted aryls lower yields were observed. This was attributed to a competing zinc catalysed reduction of the nitro groups. It was found that removal of excess zinc before Negishi cross-coupling gave greatly improved yields, with an increase from 24% to 45% in the case of 1-iodo-4-nitrobenzene (Scheme 4, **14d**).

In order to make the transformation as synthetically relevant as possible widening the scope of the haloaryl component of the Negishi cross-coupling was elaborated upon in 2008.[36] Taking inspiration from the reported reaction of a serine derivative **1** and a bromo-substituted naphthalene by Szczepankiewicz *et al.* (Scheme 5)[37] it was subsequently demonstrated that a wide range of bromides were applicable to the Negishi cross-coupling (Scheme 6).



Scheme 5 Synthesis of a naphthyl-appended amino acid precursor by Szczepankiewicz *et al.*[37]



Scheme 6 Negishi cross-couplings of aryl bromides with an iodo serine derivative.

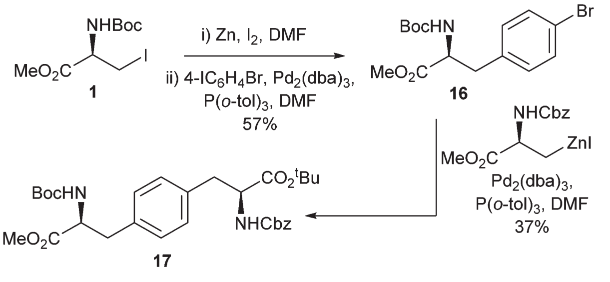
Yields for the cross-coupling reaction when an aryl bromide was employed were lower across all examples compared to their iodo equivalents.[36] However, it should be noted that aryl bromides are often cheaper and more widely available than their corresponding iodides.

By exploiting the differences in cross-coupling reactivity between aromatic iodides and aromatic bromides it was demonstrated that asymmetrical bis-amino acids could be successfully synthesised. For example, the bis-amino acid **17** (Scheme 7) was synthesised through a double cross-coupling process in a 21% overall yield. This was an improvement over the previously reported palladium-catalysed Suzuki–Miyaura coupling approach to form asymmetrical biphenyl bis-amino acids which was found to return racemic products.[38]

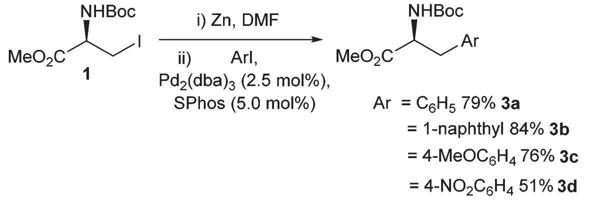
Biarylphosphine ligands such as SPhos are known to increase the rate and yield of palladium-catalysed reactions.[39] These ligands are believed to stabilise monoligated Pd(0), and in addition, have the ability to stabilise Pd(II) centres.[39,40] It was found that an active catalyst formed from 1 : 1 SPhos to $Pd_2(dba)_3$ led to improved yields (compared to earlier reports) of Negishi cross-coupled phenylalanine derivatives **3a–d** (Scheme 8).[41]

Interestingly it was found that when 2-iodoaniline was used in the presence of SPhos the expected amino acid derivative was not delivered and instead a lactam **18** was formed in good yield (85%) (Scheme 9).

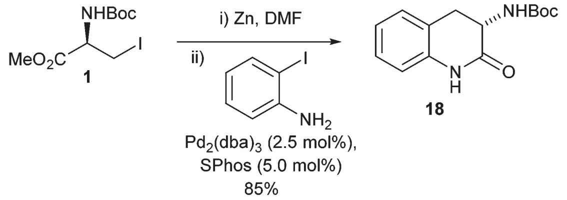
Jackson's group built upon the observation that SPhos improved the yields of Negishi cross-couplings. By taking inspiration from their work on the kinetics of β-elimination, the Boc protecting group (see mechanistic studies)[42] was



Scheme 7 Synthesis of a bis(amino acid) derivative *via* a double Negishi cross coupling strategy.



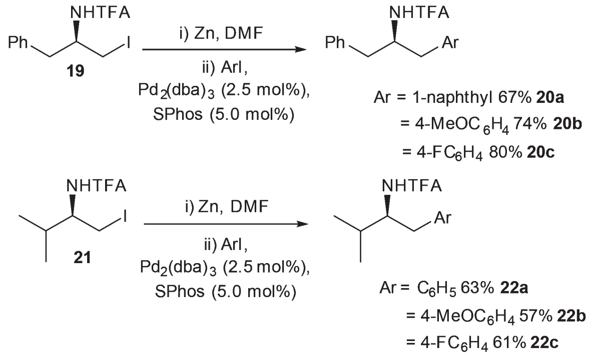
Scheme 8 Improved cross-coupling conditions using SPhos reported by Jackson and co-workers.[41]



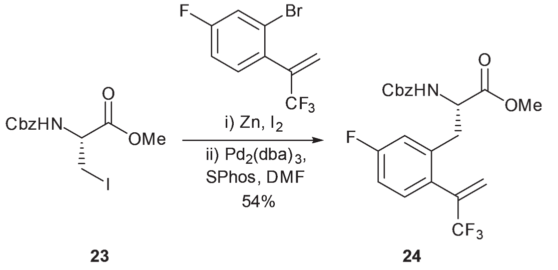
Scheme 9 Unexpected lactam formation observed in the cross-coupling of an iodoaniline with an iodo serine derivative.

replaced with a trifluoro-acyl (TFA) group (Scheme 10).[43] The TFA protecting group had been shown previously to perturb the alkyl zinc halide from undergoing β-elimination, (see later section on mechanistic studies for further information) so it was hoped that the combination of SPhos and a TFA protecting group on the zinc halide would lead to improved reaction conditions for the synthesis of phenylethylamine derivatives. TFA-protected zinc iodides derived from phenylalanine **19** and valine **21** were shown to react smoothly with a range of aryl iodides, delivering good to excellent yields of aryl appended protected amines **20a–c**/**22a–c**.

The synthesis of trifluoromethyl appended aromatic amino acids were reported by Featherston and Miller (Scheme 11).[44] Cross-coupling was successfully carried out between Cbz-protected iodide **23** and a fluoro-aromatic to give **24** in a 54% yield. The aromatic amino acid **24** was then successfully transformed into the corresponding ketone through treatment with ozone. The peptides formed in the study were found to be catalytically active in the oxidation of substituted styrenes to their corresponding epoxides. In addition to their applications in catalysis, fluorinated amino acids have also been shown to be useful as biophysical probes and as structural components in peptide sequences.[45]



Scheme 10 Amines prepared from amino acids by Negishi cross coupling, **19** and **21** prepared from phenylalanine and valine respectively in two steps.



Scheme 11 Synthesis of fluoroaromatic amino acid precursor for application in oxidation of substituted styrenes, Featherston and Miller.[44]

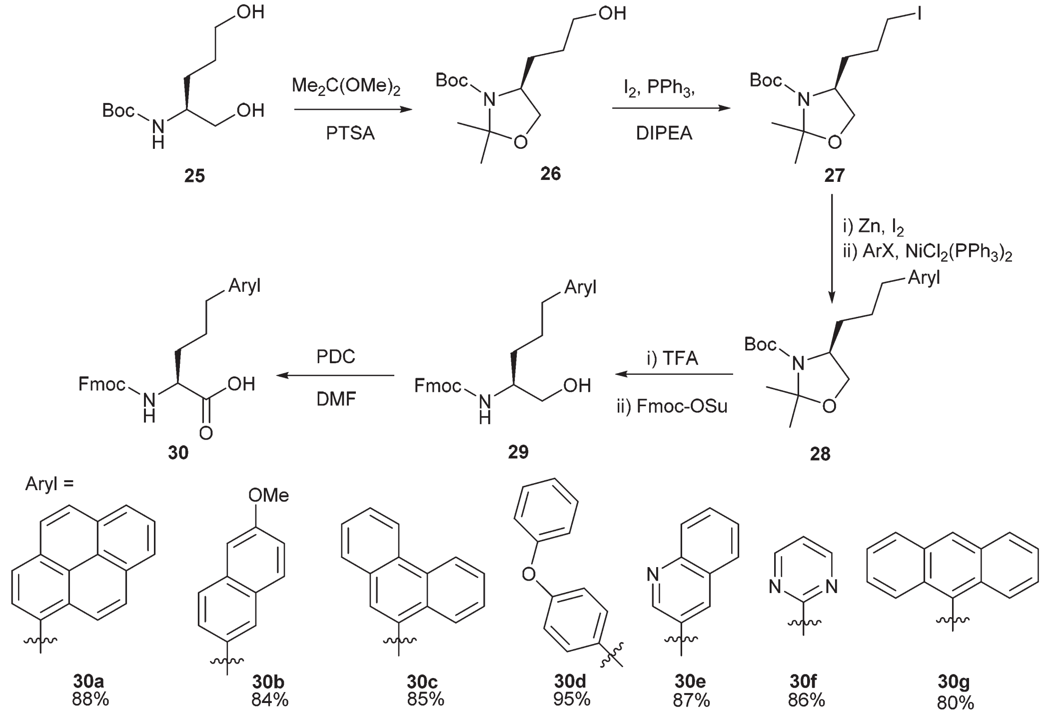
Synthesis of heteroaromatic amino acids

Drug development and discovery often utilise heteroaromatic cores to deliver potent biological activity,[46,47] and elaboration of heterocyclic cores with other moieties is a cornerstone of fragment-based drug discovery (FBDD).[48–50] Within this context heteroaromatic amino acids have been shown to be valuable building blocks for the synthesis of many biologically active compounds.[51–53] The Negishi cross-coupling is one way in which heteroaromatic-appended amino acids can be synthesised in relatively few steps with great modularity.

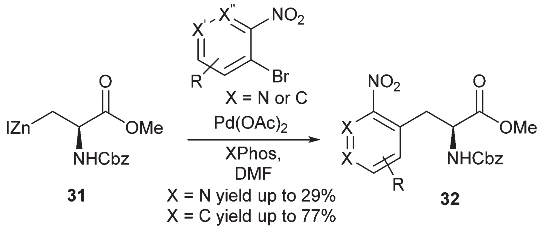
Synthesis of heteroaromatic amino acid derivatives formed through Negishi cross-coupling was reported by Göbel and co-workers.[54] Negishi cross-coupling was successfully carried out using a range of aryl bromides and iodides with oxazolidine **27** (Scheme 12). Heteroaromatics such as quinoline **30e** and pyrimidine **30f** were found to be amenable to the methodology, and the inclusion of commonly used protecting groups (Boc and Fmoc) allowed the formed novel amino acids to be incorporated into longer peptide sequences by solid phase peptide synthesis (SPPS).

A detailed study into the synthesis of *ortho*-substituted nitroaromatic containing amino acid derivatives was carried out by Tuttle *et al.* (Scheme 13).[55] Reaction optimisation between 1-iodo-2-nitrobenzene and iodozinc compound **31** showed that $Pd(OAc)_2$ in combination with XPhos in a 1 : 2 ratio gave a 92% yield of the desired cross-coupling product. In addition, it was found that 1-chloro-2-nitrobenzene was also amenable to cross-coupling in 87% yield. A range of *ortho* and multiply-substituted nitro-bromobenzenes and pyridines were used as cross-coupling partners with iodozinc compound **31**. Yields for nitropyridines ranged between 22% and 29% whilst nitrobenzenes ranged between 41% and 77% yield.

Using these novel protected amino acid derivatives, it was possible to deliver the intended hydroxamic acid targets **35**



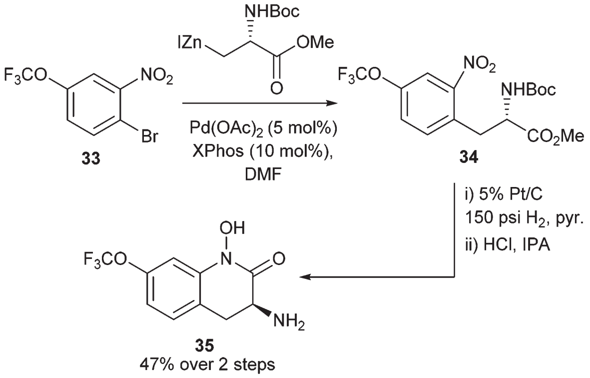
Scheme 12 Synthesis of aromatic and heteroaromatic amino acids.



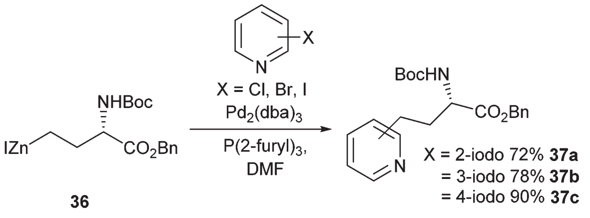
Scheme 13 Nitro-aromatic and heteroaromatic protected amino acid derivatives, Tuttle *et al.*[55]

(Scheme 14) (similar to the species observed in Scheme 9). These heterocyclic motifs were of interest for their potential biological activity and the developed methodology allowed potential access to a library of these hydroxamic acids.

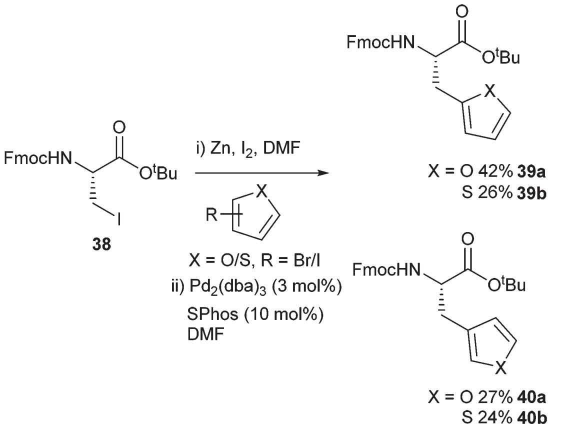
In 2014 Usuki *et al.* reported the improved Negishi cross-coupling of halopyridines with an iodozinc species derived from aspartic acid (Scheme 15).[56] Previous work such as that reported by Tuttle *et al.* (Scheme 13) had shown that yields for pyridine cross-coupling products significantly lagged behind their non-heteroaromatic equivalents.[57] After extensive reaction optimisation, a catalytic system of $Pd_2(dba)_3$ in combination with a P(2-furyl)$_3$ ligand was shown to be the best for the cross-coupling of halopyridines, with a 90% yield recorded in the reaction between 4-iodopyridine and **36**. In moving to bromo-substituted pyridines lower yields were recorded for all substrates, with 2–3- and 4-bromopyridines giving 44%, 33% and 23% yields respectively. Chloropyridines, regardless of halide position on the ring, were found to be ineffectual in all



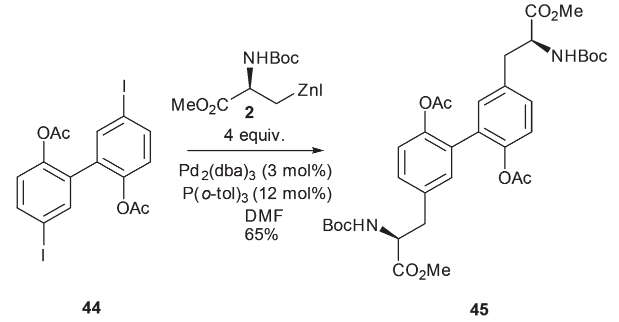
Scheme 14 Synthesis of Boc-protected nitro-aromatic-appended amino acids and subsequent cyclisation to yield novel hydroxamic acids by Tuttle *et al.*[55]



Scheme 15 Synthesis of pyridine-containing amino acids *via* Negishi cross-couplings, Usuki *et al.*[56]



Scheme 16 Furyl and thienyl-appended amino acids synthesised using Negishi cross-coupling, Cobb and co-workers.[58]



Scheme 18 Synthesis of a bi-aryl, bis(amino acid), Jackson and co-workers.[60]

cross-coupling reactions attempted. The Negishi cross-coupling of halopyridines would be utilised in the synthesis of complex pyridinium amino acids (see later section, Scheme 24).

The ability to append furyl and thienyl functionalities onto amino acids was reported by Cobb and co-workers in 2015 (Scheme 16).[58] The synthesis of 2-thienyl-alanine was achieved in a moderate 42% yield but this was an improvement over the previously reported, 10% yield.[59] Both Boc and Fmoc protecting groups were shown to be tolerated by the cross-coupling conditions. A Boc-protected 2-furyl derivative was subsequently shown to be stable in a (Benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PyBOP) mediated peptide coupling.

Synthesis of complex amino acids

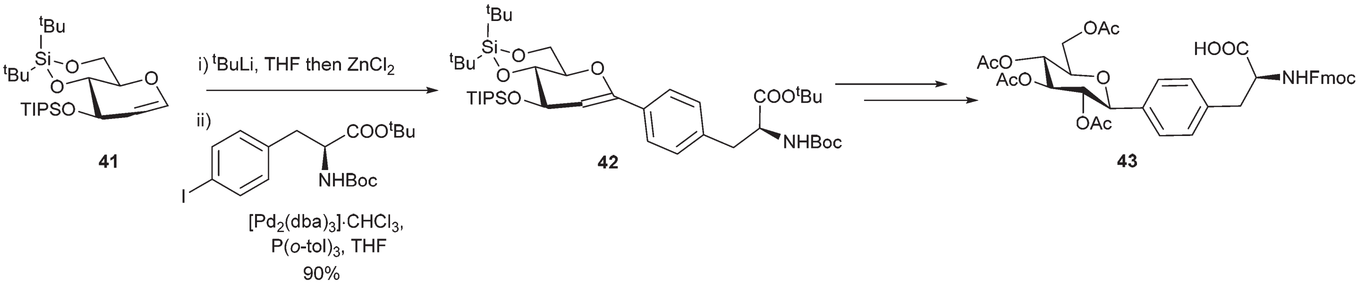
Beyond aromatic and heteroaromatic examples, the Negishi cross-coupling reaction has been used to prepare a wide range of complex amino acids.

The formation of biphenyl-linked amino acids and biphenyl amino acid derivatives can be easily achieved using a cross-coupling approach (Scheme 18).[60] The synthesis of the macrocyclic tripeptide K13[61] and a non-natural macrocyclic protease inhibitor used this approach.[62] Building upon these studies the synthesis of biphenyl linked amino acids was reported where a strategy of coupling iodosubstituted bi-aryls with alkyl zinc reagents was adopted. Negishi cross-coupling was successfully carried out between iodozinc L-serine derivative **2** and a range of mono- and diiodo-substituted bi-phenyls.

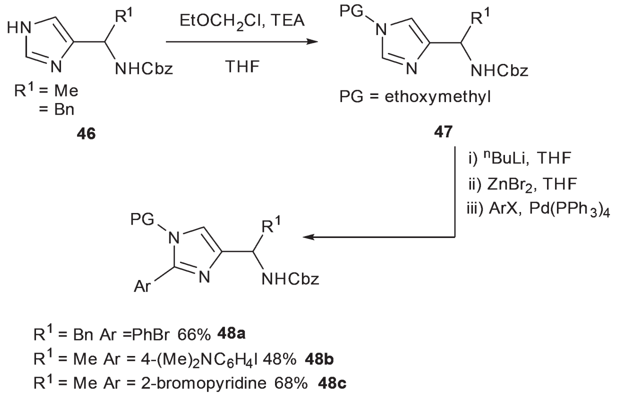
The reaction was found to be applicable to both acyl and benzyl protecting groups on the bi-phenyl moiety. However, it was found that a large excess (4 equiv.) of the iodozinc species was required in order to achieve a satisfactory yield of 65% of the biaryl derivative **45** (Scheme 18).

Glycoproteins have been shown to be critical to cell adhesion,[63,64] differentiation[65] and growth, and they have also been used as new targets for therapeutics and diagnostics.[66] Ousmer *et al.* utilised a Negishi cross-coupling to form a *p*-(C-glucopyranosyl)phenylalanine derivative (Scheme 17).[67] An iodo-substituted phenylalanine derivative was successfully coupled to a glucal **41** in an excellent 90% yield. This was then further elaborated by stereo-selective hydroboration to yield the desired glucose modified phenylalanine **43** in a 37% overall yield.

Negishi and Suzuki–Miyaura cross-couplings were shown to be amenable to the preparation of imidazoles derived from amino acids (Scheme 19).[68] Imidazoles derived from (*S*)-Ala, (*S*)-Leu and (*S*)-Phe **46** protected with ethoxymethyl groups gave substrates **47** which were found to readily undergo Negishi cross-couplings to form corresponding bi-aryl systems.



Scheme 17 Synthesis of a *p*-(C-glucopyranosyl)phenylalanine derivative.

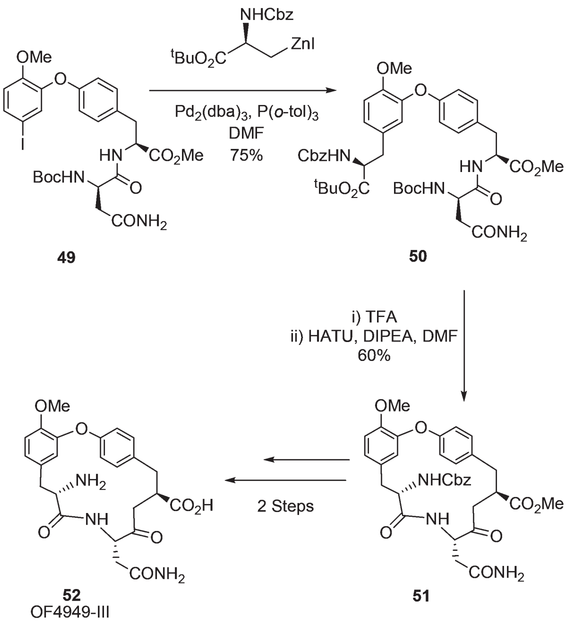


Scheme 19 Derivitisation of imidazoles from amino acids by Negishi cross-coupling, Marek *et al.*[68]

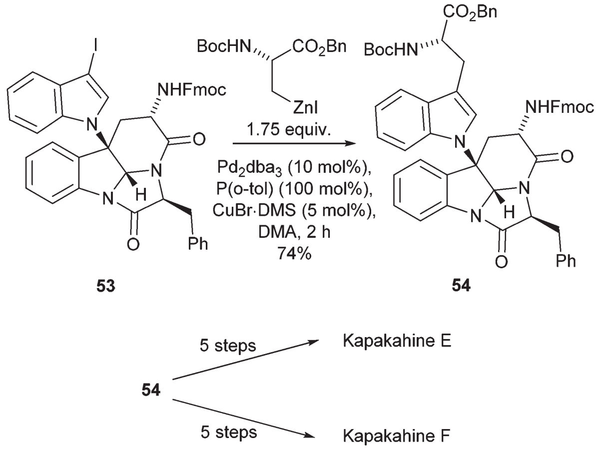
The bi-aryl protected amines **48a–c** were successfully obtained in yields ranging from 34% to 88% (Scheme 19).

Jackson and co-workers would revisit the synthesis of the macrocyclic peptide K13[61] and expand their scope to the cyclic peptide OF4949-III **52** in 2009.[69] Building on their earlier synthesis of K13 and their reported Negishi-based methodology for bi-aryl linked amino acids,[60] Jackson *et al.* reported an intramolecular Negishi strategy to afford K13 and a Negishi cross-coupling key step synthesis of OF4949-III (Scheme 20). Utilising this approach OF4949-III **52** was synthesised in 12 steps with an overall yield of 20%.

Other natural products have also been successfully synthesised using Negishi cross-couplings of amino acid building blocks as a key synthetic step. The Kapakahine family of natural products has shown promising preliminary biological activity against P388 murine leukemia cells and thus accessing these compounds was of significant interest.[70] The synthesis of Kapakahine E and F, by Espejo and Rainier utilised a Negishi cross-coupling to form a key intermediate **54** which was subsequently taken through two end game synthetic routes to yield the two natural products (Scheme 21).[70]



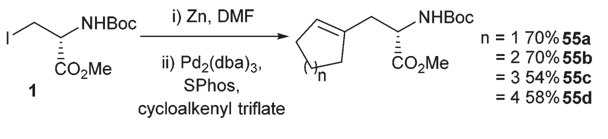
Scheme 20 Synthesis of cyclic peptide OF4949-III, Jackson and co-workers.[69]



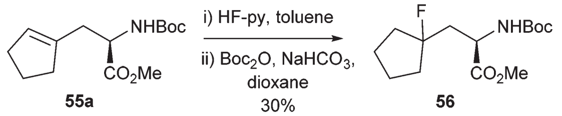
Scheme 21 Synthesis of Kapakahine E and F, Espejo and Rainier.[70]

Negishi cross-couplings that can utilise triflates in the place of the halide component have been widely utilised in mainstream organic synthesis.[71,72] Within the field of peptide chemistry it was reported that a $PdCl_2(PPh_3)_2$ mediated cross-coupling between iodozinc reagents and cycloalkenyl triflates could be carried out, but the yields obtained were only moderate, ranging between 41% and 46%.[73] The Negishi cross-coupling of iodozinc compounds with cycloalkenyl triflate derivatives was also reported by Jackson and co-workers in 2012 (Scheme 22).[74] In this study, the addition of a phosphine ligand (SPhos), in combination with a $Pd_2(dba)_3$ catalyst, gives rise to an increase in the yield of the cross-coupling reaction product to 70% for the cyclopentenyl and cyclohexenyl derivatives **55a**/**b**.

Yields for cycloheptenyl and cyclooctenyl products **55c**/**d**, however, were moderate at 54% and 58%, respectively. This led the authors to propose that the addition of lithium chloride could be advantageous. Lithium chloride had been shown previously to increase the yields in Stille reactions, and can increase the reactivity of organozinc halides.[75] Indeed, the addition of 1.8 equivalents of LiCl to the Negishi cross-coupling reaction mixture led to increased yields for the cycloheptenyl and cyclooctenyl derivatives **55c**/**d**, boosting yields to 62% and 63%, respectively.



Scheme 22 Cycloalkenyl-protected amino acid derivatives, Jackson and co-workers.[74]

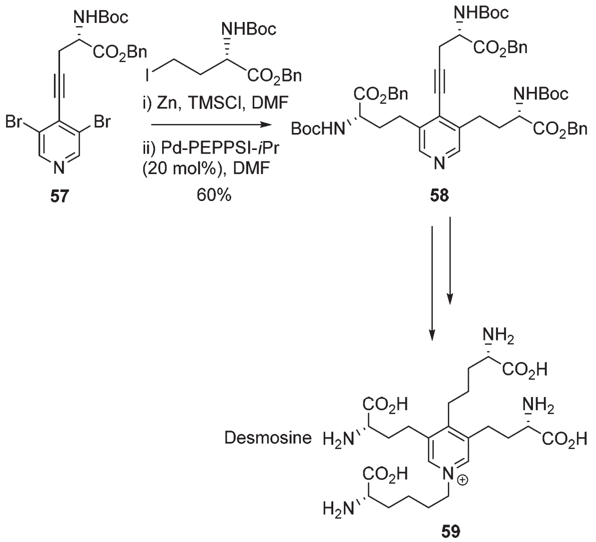


Scheme 23 Fluorination of cycloalkenyl-protected amino acid derivatives.

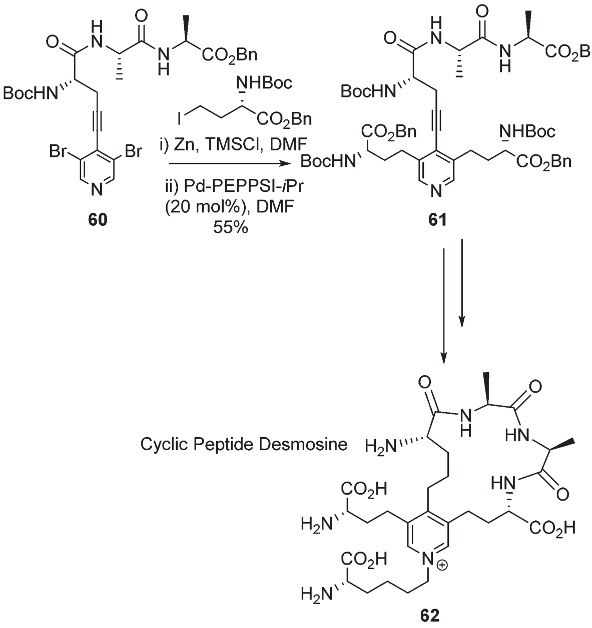
In addition to the Negishi methodology developed it was shown that the cross-coupled product **55a** could react with HF pyridine to furnish the fluoro compound **56** in 30% isolated yield (Scheme 23). This compound had been reported earlier as a building block for an enzyme inhibitor.[76] The previous synthesis of compound **56** had been relatively low yielding and had required a chiral resolution step.[77] The cross-coupling methodology therefore offered a simpler and more efficient synthesis of these fluorinated motifs.

The Negishi cross-coupling of pyridines was extended to bis-halo pyridines by Usuki and co-workers (Scheme 24).[78] Utilising a di-bromo-substituted pyridine **57** a double Negishi and Sonogashira cross-coupling was employed to garner key intermediate **58**, which was further elaborated to yield desmosine **59**. In the same report, a deuterated version of desmosine was also successfully synthesised following the same cross-coupling strategy. Desmosine is a biomarker for degradation of elastin-containing tissues, which is a symptom of diseases such as atherosclerosis, aortic aneurysm, cystic fibrosis and chronic obstructive pulmonary disease (COPD).[79–81] The synthesis of desmosine therefore is of importance for drug discovery and the rapid diagnosis of diseases such as COPD.

In 2017 Usuki and co-workers elaborted their synthesis of Desmosine to build it into a cyclic peptide (Scheme 25).[82] This work was driven by the fact that the proposed stuctures of elastin suggest cross-linkage through Desmosine.[83,84] Through the use of a Desmosine analogue the cross-linking motif within elastin was hoped to be probed. Usuki and co-workers utilised the same general strategy to build the Deomsine core as they had previously published.[78]



Scheme 24 Synthesis of Desmosine *via* a Sonogashira, double Negishi cross coupling strategy.



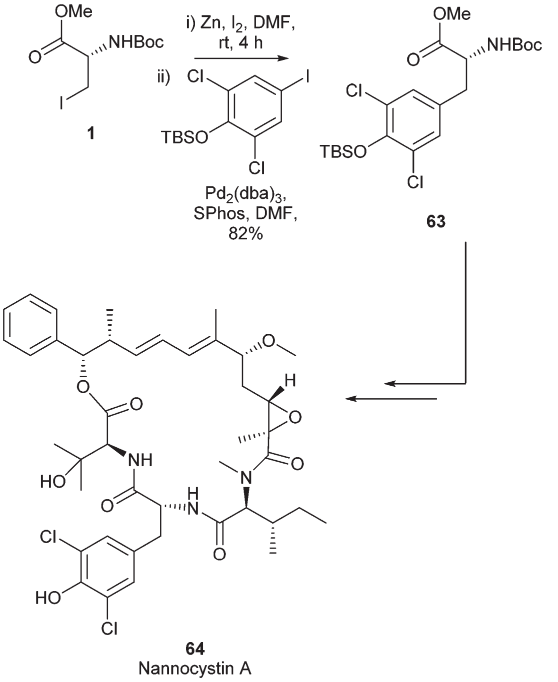
Scheme 25 Synthesis of a cyclic peptide derivative of Desmosine, Usuki and co-workers.[82]

A Sonogashira cross-coupling afforded the intermediate **60** which was elaborated with a double Negishi coupling to afford intermediate **61**. This intermediate was then successfully cyclised thtough an amide coupling reaction which led to the target compound **62**. The overall synthesis gave the desired cyclic desmosine derivative in a 0.8% overall yield from L-alanine.

In 2017 the total synthesis of Nannocystin A **64** was reported by Liu *et al.*[85] Within this report a Negishi cross-coupling of an iodo serine derviative was employed to build the key fragment **63** (Scheme 26). The final natural product was delivered with a longest linear sequence of 11 steps in a 5.3% overall yield. Nannocystin A **64** has been found to possess potent biological activity. It has been shown to be an inhibitor of elongation factor 1 and inhibits cancer cell growth.[86] The Negishi cross-coupling reaction to form a novel amino acid derivative was vital to access this potent natural product synthetically.

Mechanistic studies

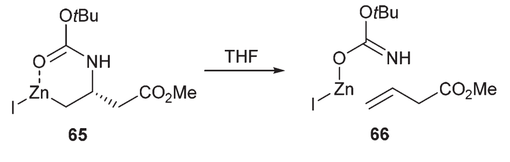
Several mechanistic studies have been undertaken to try and gain fundamental knowledge of the reactivity of alkyl zinc amino acid derivatives. Using a range of analytical techniques, the species responsible for catalysis and mechanistic pathways have been probed. From these studies a greater understanding



Scheme 26 Total synthesis of nannocystin A, Liu *et al.*[85]

of the workings of Negishi cross-couplings of iodo amino acids has been established.

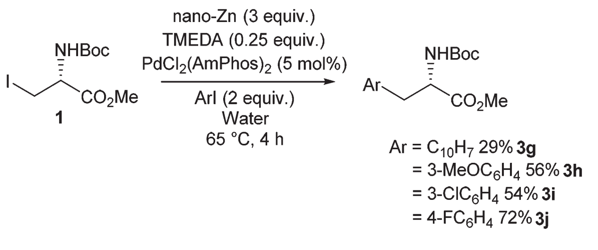
One of the major problems in the synthesis of β-amino acids using Negishi cross-coupling is that the iodozinc cross-coupling partner (derived from species such as aspartic or glutamic acid) is intrinsically susceptible to β-elimination to form an alkene. In order to understand these problems, NMR spectroscopy was utilised to probe the decomposition of β-amidozinc reagents. NMR kinetic studies showed that the rates of β-elimination in both THF-d_8 and DMF-d_7 were first order and pointed towards a unimolecular rate-limiting step. In addition, it was observed that the rate constant in the case of DMF was four times smaller than that for THF. Therefore the elimination process is significantly perturbed in DMF. Calculation of the activation parameters led to the conclusion that the elimination process was *syn* in nature, invoking an intramolecular coordination between the carbamate and the zinc centre (Scheme 27). DMF therefore is believed to compete with the carbamate for zinc, thus slowing the rate of elimination.



Scheme 27 Syn elimination of Boc protected amidozinc reagents.

In 2003 it was reported that a β-amidozinc reagent was more resistant to elimination when a better leaving group was employed.[87] Jackson and Rilatt further studied this kinetic stability and reactivity of β-amino alkyl zinc iodides in 2008.[88] They found that the *N*-protecting group on the zinc iodide was critical in determining the rate of β-elimination. Boc protecting groups were found to increase the rate of elimination, and from this it was theorised that the carbonyl group (within the carbamate) was competing with the ester for coordination with zinc, leading to increased elimination. Replacing the Boc group with a TFA group perturbed the rate of elimination. The lower Lewis basicity of TFA on its carbonyl group helps prevent coordination to the zinc, and thus elimination. On top of this, it was observed that upon changing the Boc group for TFA, the rate constant changed from being first order to second order, indicating that the TFA elimination pathway follows a different mechanism from the Boc elimination. In the same report the reactivity of the β-amino alkyl zinc iodides towards Negishi cross-coupling was also studied. It was found that the *N*-protecting group made little difference to the rate of cross-coupling with the main factor being the proximity of the ester from the Zn site. It was concluded that a TFA *N*-protecting group offers much greater stability toward β-elimination whilst not affecting the rate of Negishi cross-coupling.

Negishi cross-coupling was found to be applicable to aqueous environments. It was reported that the presence of tetramethylethylenediamine (TMEDA) allows the Negishi cross-coupling of phenylalanine derivatives to be successfully carried out in the presence of water (Scheme 28).[89] Being able to carry out Negishi reactions in water is of significant interest to peptide chemists, as it allows the post-translational modification of peptides. It was found that the TMEDA helps prevent protonation of the alkylzinc iodides in water. It was proposed that the stabilisation occurs due to the TMEDA inducing ionisation in the zinc-iodine bond. This hypothesis was supported by evidence from tandum mass spectometery, infrared multiphoton dissociation and DFT calculations. Conditions for the successful synthesis of alkylzinc iodides and subsequent Negishi coupling in water were probed, and it was found that the use of nano zinc in combination with TMEDA and a $PdCl_2(AmPhos)_2$ gave good yields ranging between 28% and 73% of phenylalanine derivatives.



Scheme 28 Negishi cross coupling in water of an iodo serine derivative, Jackson and co-workers.[89]

Conclusions

The Negishi cross-coupling reaction has been shown to be a highly versatile reaction allowing an expedient route to the synthesis of many unnatural amino acids. Since the pioneering work of Jackson and co-workers advances in available reagents (*e.g.* new ligands) has led to an increase in substrate tolerance and product yields. In addition mechanistic studies have helped researchers to understand the requirements for successful cross-couplings across a range of substrates and this has in turn allowed access to more novel unnatural amino acids than ever before. The ability to prepare novel aromatic, heteroaromatic and complex amino acids opens up a myriad of new potential applications for these motifs. For example, as highlighted in this review, unnatural amino acids accessed *via* Negishi cross-couplings have been exploited in the fields of natural product synthesis, drug discovery, materials/polymer chemistry and catalysis.

Conflicts of interest

There are no conflicts to declare.

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