

Review

The Suzuki–Miyaura Cross-Coupling as a Versatile Tool for Peptide Diversification and Cyclization

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Abstract: The (site-selective) derivatization of amino acids and peptides represents an attractive field with potential applications in the establishment of structure–activity relationships and labeling of bioactive compounds. In this respect, bioorthogonal cross-coupling reactions provide valuable means for ready access to peptide analogues with diversified structure and function. Due to the complex and chiral nature of peptides, mild reaction conditions are preferred; hence, a suitable cross-coupling reaction is required for the chemical modification of these challenging substrates. The Suzuki reaction, involving organoboron species, is appropriate given the stability and environmentally benign nature of these reactants and their amenability to be applied in (partial) aqueous reaction conditions, an expected requirement upon the derivatization of peptides. Concerning the halogenated reaction partner, residues bearing halogen moieties can either be introduced directly as halogenated amino acids during solid-phase peptide synthesis (SPPS) or genetically encoded into larger proteins. A reversed approach building in boron in the peptidic backbone is also possible. Furthermore, based on this complementarity, cyclic peptides can be prepared by halogenation, and borylation of two amino acid side chains present within the same peptidic substrate. Here, the Suzuki–Miyaura reaction is a tool to induce the desired cyclization. In this review, we discuss diverse amino acid and peptide-based applications explored by means of this extremely versatile cross-coupling reaction. With the advent of peptide-based drugs, versatile bioorthogonal conversions on these substrates have become highly valuable.

Keywords: Suzuki–Miyaura reaction; peptide diversification; peptide cyclization

1. Introduction

The Pd-catalyzed Suzuki–Miyaura reaction has found widespread use in the synthesis of carbon–carbon bonds [1,2]. The success of this cross-coupling reaction can be attributed to the generally mild reaction conditions required and the versatility of the boron species as organometallic partners [3–9]. Compared to related C–C bond formations, the environmentally benign nature, high functional group tolerance, wide commercial availability of the reactants, and compatibility with aqueous conditions are advantageous [10–12]. As a result, various research groups have utilized and reviewed this reaction for the derivatization of complex molecules such as natural products [13–16] and nucleosides [17–23]. The mechanism of this reaction originally proposed by Miyaura and Suzuki has been revisited recently, which provides insights useful for rational reaction optimization [24–26]. Besides classical organoboronic acids, new boron-derived reagents

have been developed with improved shelf life and controlled release of reactant and stability versus deborylation during cross-coupling [4–9,27,28]. In this review, we focus on the derivatization of amino acids up to protein substrates. In general, through bioorthogonal reactions, the site-selective derivatization of peptides and proteins is possible after the incorporation of non-proteinogenic amino acids and subsequent labeling of the (bioactive) substrate [29–33]. Additionally, this cross-coupling possesses a huge potential with regards to the improvement of peptide-based therapeutics and pharmacological probes. To achieve the envisaged site-selective modification, a single residue must undergo transformation in the presence of a significant amount of other side chains or functionalities. In contrast, when multiple reactive sites are present, non-selective derivatization methods often yield less active conjugates that are difficult to separate [34]. To access the desired, pin-pointed modification, a wide array of halogenated and borylated residues (selected examples are shown in Figure 1) can for instance be incorporated in peptidic substrates, all of which allow diverse substitutions or cyclizations.

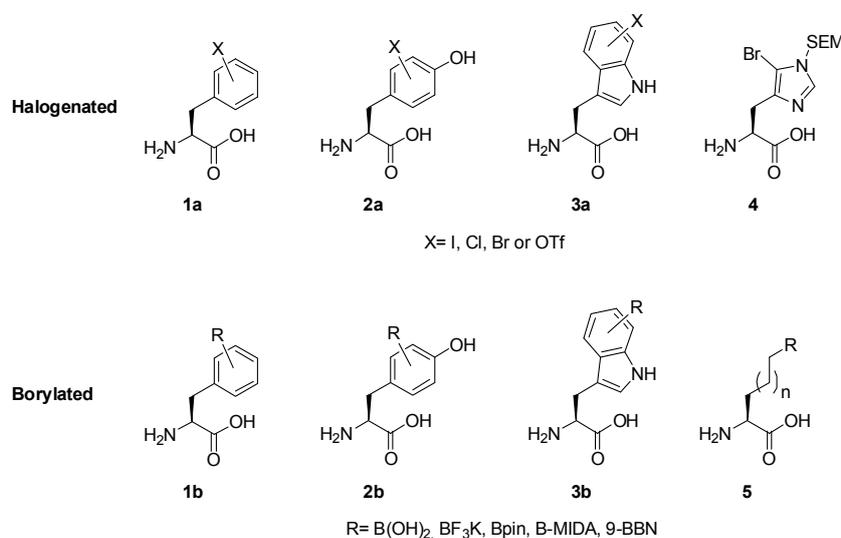


Figure 1. Representative examples of building blocks used in Suzuki–Miyaura-based derivatizations.

Halophenylalanines are generally commercially available, while (bio)synthetic methods have been developed for the preparation of halogenated tryptophans [35–38]. Boron groups are readily introduced in aromatic and aliphatic amino acids via borylation or hydroboration [39,40]. Insertion of these residues can be realized via solid-phase peptide synthesis (SPPS) methods utilizing the halogenated or borylated amino acid analogue. Next, peptide derivatization can be performed in solution-phase, after cleavage from the solid support. Alternatively, the direct Pd-catalyzed solid-phase derivatization has also been widely reported. The latter strategy offers the added value of a rapid purification by filtration, and hence removal of excess reactants, reagents, by- or side-products.

Due to the significant role that natural aromatic amino acids play in peptide-protein interactions [41], it can easily be perceived that additional interactions with the biological targets are within reach through usage of derivatized amino acids, prepared by the Suzuki–Miyaura reaction. The benefit of using non-natural amino acids has been well established [42–44], as the biological activity profile of the targeted peptide and its overall stability can be greatly enhanced through such modifications [45]. Ready access to a broad variety of unusual amino acids is therefore highly desirable for medicinal chemists, since they allow to perform structure–activity relationship studies. Hence, the Suzuki–Miyaura reaction serves as a powerful tool for peptide/medicinal chemists and it has certainly secured a place in their “toolbox” to improve peptide lead agents [45–47].

Furthermore, since both the halogen substituent and the boronate group are readily introduced, cyclization of the peptide can be achieved through Suzuki–Miyaura cross-coupling. Traditionally, cyclic peptides are often used as analogues of their linear counterparts to protect the peptide from

a premature enzymatic degradation, to stabilize secondary motifs and lock the active conformation for an improved pharmacological profile [48]. Peptide macrocyclization has thus been developed to overcome the intrinsic drawbacks of peptide therapeutics [49–52]. In this regard, various strategies have emerged for the synthesis of constrained cyclic peptides with different structural motifs emerging at the site of macrocyclization. Commonly applied strategies include disulfide or lactam bridge formation [53], ring-closing metathesis (RCM) [54], azido-alkyne cycloaddition [55], and palladium-catalyzed reactions [15,56,57]. Of specific importance to the current review are the biaryl-bridges, which gained interest for the stabilization of α -helices and β -sheets [58,59]. Interestingly, biaryl-linkages and moieties are also found in a variety of naturally occurring peptides and even synthetic drugs (e.g., Figure 2) [60,61].

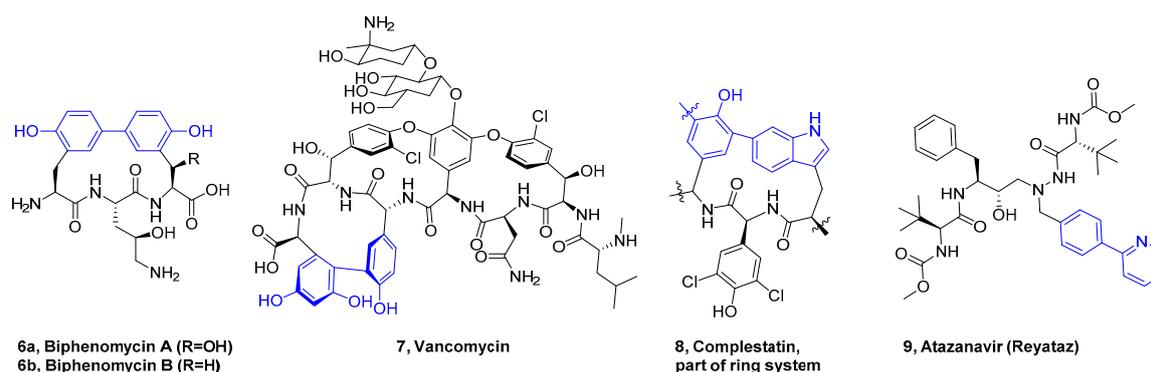


Figure 2. Naturally occurring peptides 6–8 and anti-retroviral drug Atazanavir 9 containing a biaryl moiety.

In light of the natural environment of peptide substrates, the importance of water as a (co-)solvent has been evaluated during Suzuki–Miyaura reactions applied on peptide substrates. The need for aqueous or mixed aqueous conditions is important for enabling the derivatization of unprotected amino acids or proteins, since such solvent systems ensure solubility of these complex products. The development of water soluble ligands and further improvement of catalysts for classical organic reactions [62] has encouraged peptide chemists to also explore mild conditions for amino acid/peptide derivatizations [63,64]. Such reaction conditions are preferred for amino acid(-based) substrates in order to avoid epimerization or other unwanted side reactions, while mild conditions are simply mandatory for protein substrates. Physiological conditions (37 °C, buffered aqueous solutions) are often considered to maintain the natural protein folding [63,65].

In this review, the aim is to present, in a comprehensive manner, the major advances of the Suzuki–Miyaura cross-coupling in the field of peptide chemistry. Ever since the first reports in 1992, replacement of the typical organic reaction conditions, along with developments in chemical biology, has opened a plethora of potential applications. The usefulness of this cross-coupling has been shown on simple amino acids, synthetically prepared peptides, and large protein complexes. Herein, we focus on methodology development for both solution- and solid-phase derivatizations of increasingly complex substrates. Efforts towards peptidic natural product synthesis and peptide cyclization are discussed. In the final part, several biological applications in different therapeutic areas are briefly highlighted in which the Suzuki–Miyaura reaction represented a key reaction.

2. Derivatization of Amino Acids and Peptides in Solution

2.1. Access to and Derivatization of (Pseudo)halogenated Aromatic Amino acid Substrates

Halogenated residues can be introduced in peptide sequences via replacement of aromatic amino acids by their halogenated (Cl, Br, I) or pseudohalogenated (OTf, OMs) analogues. In contrast to these aromatic amino acids bearing (pseudo)halogenated moieties, amino acid-based alkyl halides

are not used directly as substrates in the Suzuki–Miyaura reaction. To date, their use is limited to the Negishi reaction of β -iodoalanine, β -iodohomoalanine, and iodobishomoalanine with various aryl iodides, to gain access to non-proteinogenic phenylalanine analogues [66–69]. For peptides that are prepared by chemical methods, SPPS easily enables the replacement of an aromatic amino acid with a non-natural (pseudo)halogenated analogue. Most of the (pseudo)halogenated phenylalanines are available from commercial sources. In contrast, the use of halotryptophans as substrates in Suzuki–Miyaura couplings was initially hampered by their limited commercial availability (NB: pseudohalogenated tryptophans and derivatization thereof have not been reported to date). Chemical synthesis of these building blocks often lack generality and require specific procedures for each regioisomer [70–73]. In view of this issue, a straightforward procedure for the enzymatic synthesis of halogenated tryptophans was described via use of tryptophan synthase on the corresponding readily available indole analogues [37,74]. This methodology affords Gram-scale quantities of enantiomerically pure chlorotryptophans, bromotryptophans, and more recently 7-iodotryptophan [75]. Site-specific halogenases of tryptophan have also been developed for the preparation of halotryptophans. [35–38,76,77] Complex protein substrates that contain halogenated residues and which are not accessible via chemical synthesis could also be specifically obtained by means of auxotrophic strains or reassignment of stop codons [78,79]. Pioneering work by the group of P. G. Schultz expanded the genetic code via a unique tRNA/aminoacyl-tRNA synthetase pair, resulting in a solid protocol to insert 4-iodophenylalanine [80] and 4-boronophenylalanine [81]. The introduction of 4-iodophenylalanine, for example, opened the gateway for protein modification via Pd-catalyzed reactions [65,82,83].

While early cross-couplings on amino acid substrates include Sonogashira, Mizoroki–Heck, and Stille cross-couplings, the Suzuki–Miyaura reaction is most prominent in literature for the bioorthogonal derivatization of (pseudo)halogenated aromatic amino acid-containing substrates [21,84,85]. Initial work reported by Shieh et al. described the derivatization of protected L-tyrosine triflate **10** with different aryl boronic acids [86]. By combination of Pd(PPh₃)₄ and anhydrous K₂CO₃ in DMF (Figure 3A), racemization was observed (an ee as low as 66% was observed). However, by changing base to Et₃N, racemization could be avoided, but the reaction time was significantly increased to two days. Improvement of the reaction conditions was realized by use of toluene and anhydrous K₂CO₃, which combined shorter reaction times with excellent yields and high optical purity. Derivatization of halogenated substrates **12** (Figure 3B) was first described by Burk and coworkers, and their pioneering work involved biphasic conditions (DME/aqueous base), and di- and tripeptide substrates [87]. During their optimization, it was found that using Pd(OAc)₂ in combination with P(*o*-tol)₃ yielded high conversion and no observable amounts of racemization. These conditions could be applied on protected 2-,3- and 4-bromophenylalanine **12**, whereas the successful derivatization of several dipeptides and a tripeptide (containing methionine) demonstrated the versatility of this reaction. Kotha et al. further explored the derivatization on Boc-Phe(4-I)-OMe and small peptides (up to five residues: Boc-Ala-Leu-Phe(4-I)-D-Val-Val-OMe, not shown) [88]. In their work, Pd(PPh₃)₄ in a mixed THF/toluene solvent system, combined with an aqueous solution of inorganic base (Na₂CO₃), afforded cross-coupled products starting from protected 4-iodophenylalanine with excellent yields and no reported racemization.

In following years, the substrate scope was further extended. Wang et al. showed that an asymmetric hydrogenation of **14**, (with (S/S)/(R/R)[Et-DuPHOS-Rh]OTf), followed by Suzuki–Miyaura cross-couplings on protected 5-bromotryptophan **15**, afforded ready access to a series of novel tryptophan analogues **16** (Figure 4A) [89]. Intermediate **14** was prepared via Horner–Wadsworth–Emmons olefination of 5-bromo-3-formylindole and phosphonate (MeO)₂P(O)CH(NHCbz)-COOMe. The protected 5-bromotryptophan **15** was then submitted to similar conditions, as described by Burk [87], yielding bulky and hydrophobic 5-aryltryptophans (Figure 4A). In addition, Espuña published the first derivatization of an iodinated aspartame **17**, bearing no protecting group at the *N*-terminus and a side chain carboxylic acid (Figure 4B) [90].

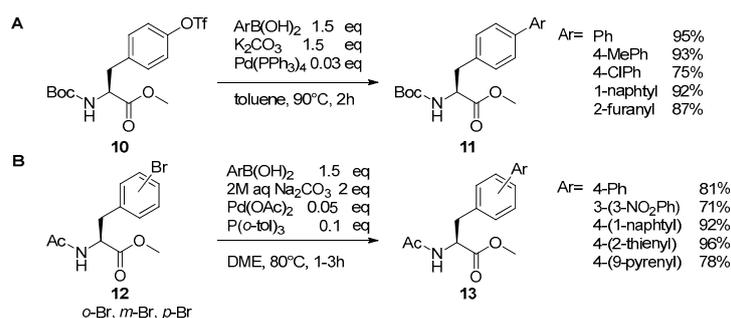


Figure 3. (A) First report of Suzuki–Miyaura reaction on 4-triflyloxyphenylalanine [86]. (B) Protected bromophenylalanines as substrates for cross-coupling.

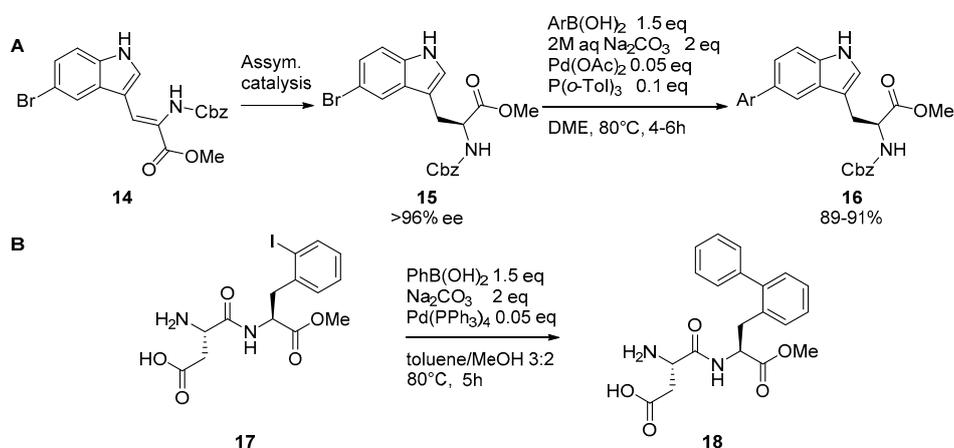


Figure 4. (A) Access to 5-aryltryptophans **16** via sequential asymmetric hydrogenation and Suzuki–Miyaura reaction. (B) Iodinated aspartame **17** transformed via cross-coupling.

Work published by Limbach et al. showed that protected 4-bromo- β^3 -homophenylalanine **19** could be derivatized in mixed organic/aqueous (toluene/H₂O 8:1) conditions with a catalyst loading as low as 5 mol % (Figure 5A) [91]. The substrate scope was further expanded by Knör and coworkers via introduction of protected 3-iodo-L-tyrosine as a substrate [92]. In their work, biphasic conditions (DME/aq. Na₂CO₃) were applied in combination with Pd(OAc)₂ and P(*o*-tol)₃. Under these conditions, it was shown that protection of both the main chain termini and the phenol group was required. Cerezo reported the synthesis of 5-arylhistidines **22** under microwave conditions [93]. Ac-His-OMe was first treated with *N*-bromosuccinimide (NBS) and subsequently protected with a 2-(trimethylsilyl)ethoxymethyl (SEM) group, to yield **21**. Due to the coordination potential of the imidazole ring of histidine, elevated reaction temperatures, combined with relatively high catalyst loading (up to 40 mol %) and KF as a base, were required (Figure 5B). Under these optimized conditions, a series of novel 5-substituted histidines **22** were prepared, but only in moderate yields and facilitated under microwave (MW) conditions. In an attempt to suppress the racemization of protected 3-bromo-4-methoxyphenylglycine (not shown), a substrate sensitive for racemization, Prieto and colleagues studied the Suzuki–Miyaura cross-coupling of protected phenylglycine with various aryl boronic acids [94]. It was found that, by means of mild bases, such as sodium succinate and potassium acetate, racemization could be avoided. Recently, Dumas et al. proposed the use of Pd-nanoparticles (ca. 5.6 nm diameter) as catalyst for Suzuki–Miyaura reactions in aqueous media for the derivatizations of Boc-protected halophenylalanine as the substrate [95]. In their work, the nanoparticles were stabilized on the surface of larger poly(D,L-lactide-*co*-glycolide)-block-poly(ethylene glycol) copolymer nanoparticles (PLGA-PEG

NPs, ca. 158 nm diameter). These nano-assemblies were found to be excellently suited to catalyze the Suzuki–Miyaura coupling (1 mol %) of brominated and halogenated amino acids with arylboronic acids at 37 °C for 18 h (98% conversion) (Figure 5C). Remarkably, when potassium phenyltrifluoroborate or phenylboronic acid MIDA-ester (*N*-methyliminodiacetic ester) were used, respectively 4% and no cross-coupled product was found. When cyclic triolborate derivatives (for example, potassium 4-methyl-1-phenyl-2,6,7-trioxa-1-borate-bicyclo-[2.2.2]-octane **24**) were used, the reaction rate was improved in comparison with boronic acids. Moreover, the reaction could be carried out in slightly acidic media (phosphate buffer, pH = 6.0), which can be beneficial for substrates containing base-sensitive groups.

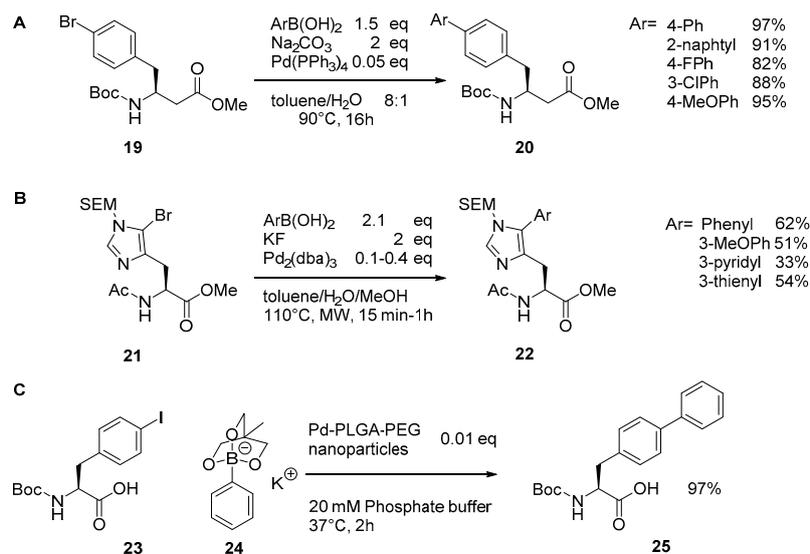


Figure 5. (A) Derivatization of β^3 -homophenylalanine **19** in mixed aqueous conditions. (B) Protected 5-bromohistidine **21** as a substrate for arylation. (C) Cross-coupling with palladium nanoparticles yielding **25**.

The derivatization of unprotected halotryptophans was first described by Deb Roy et al. under purely aqueous conditions, with the aid of the water-soluble trisulfonated triphenylphosphine (TPPTS) ligand, and Na_2PdCl_4 as a precatalytic system (Figure 6A), to generate tryptophan analogues **27** with fluorescent properties [64]. As expected, the obtained yields were highly dependent on the halogen atom present ($\text{Br} > \text{Cl}$), and derivatization on the 7-position afforded low yields. Further optimization indicated that a related ligand, bearing sulfonated *m*-xylene groups instead of phenyl (TXPTS), allowed for work at a lower temperature (40 °C) while still presenting excellent yields and significantly improved conversions when introducing a phenyl substituent on the 7-position. Alteration of the ligand to sulfonated 2-dicyclohexylphosphino-2'-6'-dimethoxybiphenyl (SSPhos) was necessary to maintain the applicability of the Suzuki–Miyaura reaction on 7-Cl-tryptophans, as beautifully illustrated by derivatization of the natural product chloropacidamycin in mixed aqueous conditions (water/acetonitrile (AcN) 5:1) [96]. The synthesis of 7-vinyltryptophan **29** with potassium vinyltrifluoroborate and $\text{PdCl}_2(\text{dppf})$, starting from 7-iodotryptophan **28** in mixed aqueous conditions (Figure 6B), broadened the scope of halotryptophan derivatization, along with the derivatization of unprotected bromotryptophan and bromotryptophan-containing dipeptides [97]. Recently, Frese et al. combined a biocatalytic and regioselective tryptophan halogenation and Suzuki–Miyaura cross-coupling in a multi-step one-pot reaction [98]. The benign halogenation is performed via immobilized tryptophan 5-, 6-, or 7-halogenases using NaBr as a halogen source, followed by biocatalyst removal and subsequent Suzuki–Miyaura reaction. The cross-couplings proceeded in high conversion with either SPhos in mixed aqueous conditions or SSPhos in purely aqueous conditions (Figure 6C).

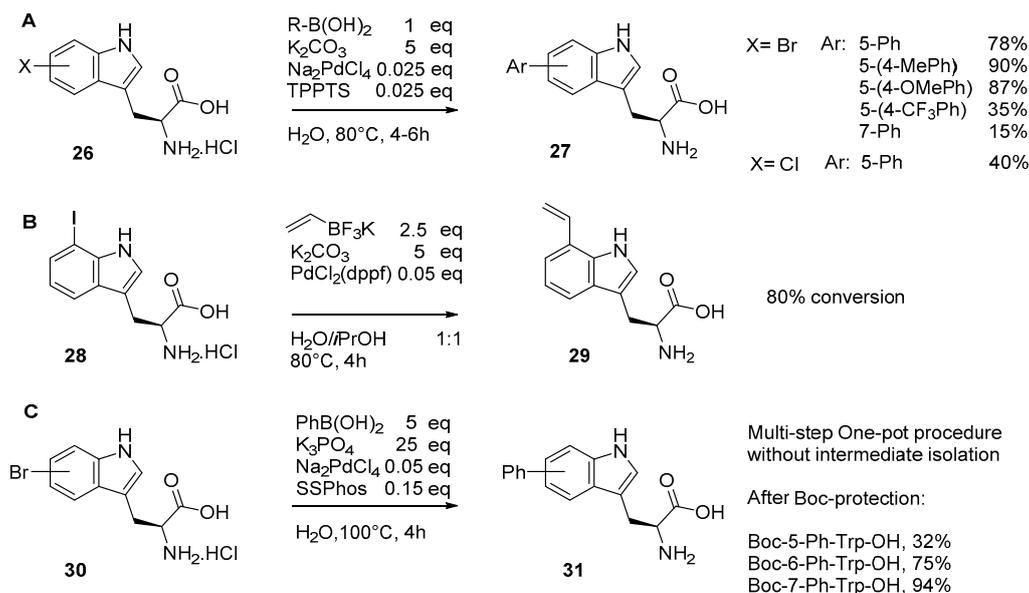


Figure 6. Derivatization of unprotected halotryptophans in aqueous conditions: (A) Arylation. (B) Vinylation. (C) Multistep one-pot biocatalytic halogenation presented 30, followed by Suzuki–Miyaura reaction.

As the Suzuki–Miyaura reaction is performed in basic conditions, the base labile 9-fluorenylmethyloxycarbonyl (Fmoc) protecting group is often not considered as part of a substrate. Nevertheless, Willemse reported Fmoc-iodophenylalanine as a substrate, and in their hands demonstrated that at 80 °C Fmoc-deprotection occurs when using PdCl₂(dppf) in mixed aqueous conditions (*i*PrOH/H₂O 1:1) with K₂CO₃ (not shown) [97]. However, by lowering the reaction temperature to 40 °C, no deprotection occurred, but the reaction only reached a maximum conversion of 80% after 24 h. Similarly, Maity et al. investigated the fluorescent properties of an amino acid containing a 4'-acetamido[1,1'-biphenyl] moiety [99]. The synthesis involved the successful Suzuki–Miyaura cross-coupling reaction of 4-acetamidophenyl-1-pinacolatoboron ester with Fmoc-4-bromophenylalanine step in 81% yield (not shown). The cross-coupling proceeded in the presence of PdCl₂ and Na₂CO₃ in a mixture of THF and ethylene-glycol (10:1) at 66 °C. Recently, Qiao and coworkers reported the one-step synthesis of Fmoc-protected aryl substituted phenylalanines 33 (Figure 7) [100]. Formation of des-Fmoc product was minimized by using relatively mild conditions (<80 °C) and an organic solvent (THF or *t*-amylOH). Microscale high-throughput screening of diverse phosphine ligands indicated that 1,1'-bis(*di-tert*-butylphosphino)ferrocene (DTBPF) was optimal in combination with Pd(OAc)₂ as Pd-source and K₃PO₄ as a base. Under the optimized conditions, no ee erosion was observed. The developed methodology proved successful for generating Fmoc-Bip (biphenyl) derivatives with both aryl boronic acids containing e-withdrawing and e-donating groups. Preliminary experiments on a Fmoc-protected pentapeptide suggested that the reaction rate was significantly reduced and after 50 h only des-Fmoc products (3:1 starting bromide vs. product) were observed.

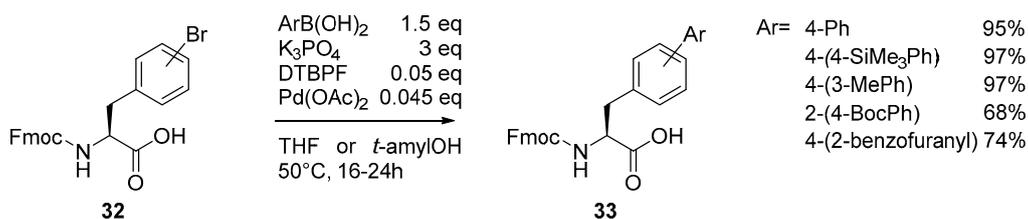


Figure 7. Synthesis of Fmoc-protected biphenylalanines 30.

2.2. Synthesis of Borylated Aromatic and Aliphatic Amino Acids and Subsequent Derivatization

Most studies of the Suzuki–Miyaura reaction on biomolecules, such as amino acids and peptides, are performed on halogenated Trp, Phe, or peptide sequences containing these residues as a consequence of their good accessibility and straightforward introduction into sequences by means of SPPS. The incorporation of borylated amino acids into peptide sequences equally allows cross-coupling with aryl or alkyl halides. Coupling with alkyl halides in particular has the added advantage of an excellent commercial availability of structurally diverse halogenated reactants and their improved stability in comparison to alkylboronic acids. The latter compounds possess low stability and limited commercial availability, and easily undergo deborylation or β -hydride elimination after transmetalation [101]. The biological stability and role of boronic acids in therapeutic peptides has already been studied in detail since this functional group has been used in protease inhibitors, boron neutron-capture therapy, and cancer therapy (e.g., Bortezomib) [102].

Multiple borylated amino acids have been synthesized, both aliphatic and aromatic residues [39,40]. Introduction of boron can be achieved through different strategies which depend on the envisaged application. Synthetic methods standardly introduce a protected analogue of a boronic acid. The preparation of pinacolyl arylboronate esters in particular has been well described, either starting from Seebach's imidazolidinone [103,104], via the Miyaura borylation of a (pseudo)halogenated phenylalanine [105–108], metal–halogen exchange [109], through direct Iridium-catalyzed borylation [110–112], or even Friedel–Crafts alkylation (selected examples are shown in Figure 8) [113]. Alternatively, direct synthesis of amino acids containing the MIDA-boronate ester group is also possible via Negishi coupling (not shown) [114].

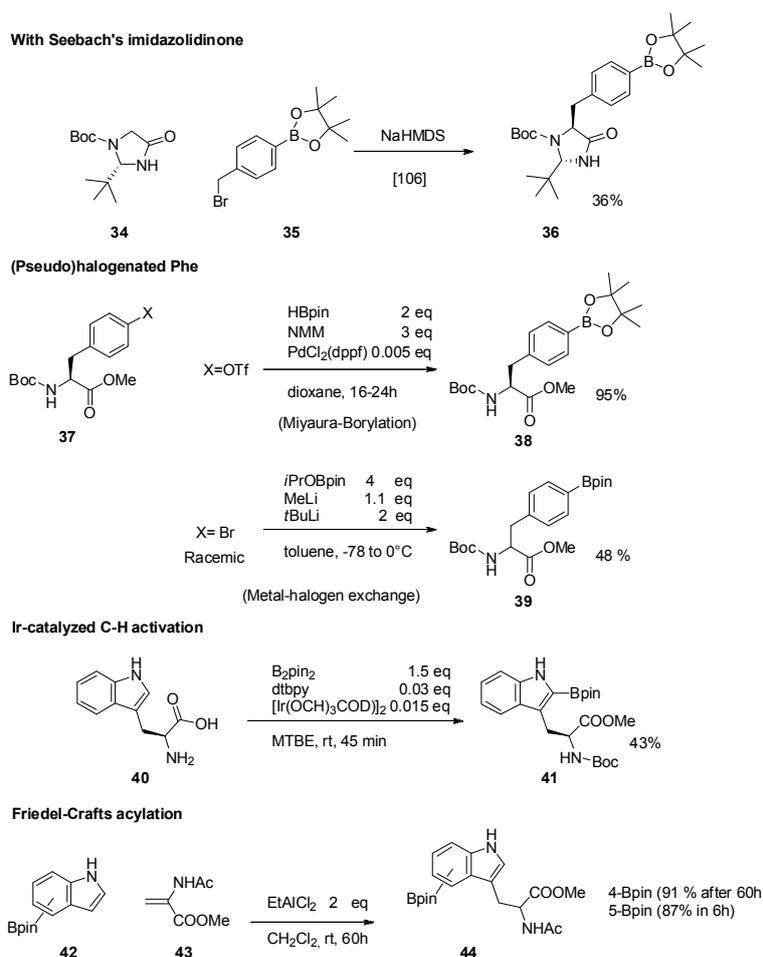


Figure 8. Representative examples of methods to prepare pinacolyl arylboronate esters.

The cross-coupling of 4-pinacolylborono-L-phenylalanine [L-Phe(4-Bpin)] **45** with aryl iodides was first reported by Satoh et al. When aryl bromides and triflates in combination with the pre-catalyst PdCl₂(dppf) were used, moderate yields resulted (Figure 9A) [103]. In the same year, an extension of this study was reported by Firooznia, describing the derivatization of racemic Boc-Phe(4-Bpin)-OEt with aryl chlorides, conversions which required the alkylphosphine-based precatalyst PdCl₂(PCy₃)₂ [104]. Their methodology was however limited to electron-donating aryl chlorides. Enantiomerically pure Boc-L-Phe(4-Bpin)-OMe was also derivatized by the same group through application of the previously published conditions of Satoh et al. [103], which used PdCl₂(dppf) in DME. It was also shown that racemic, unprotected 4-boronophenylalanine (4-BPA) could be derivatized under microwave conditions (150 °C, 5–10 min) [115]. Optimal conversion was achieved when PdCl₂(PPh₃)₂ was used in combination with Na₂CO₃ in water/acetonitrile (1:1) as a solvent. Čapek et al. investigated the cross-coupling of unprotected 4-boronophenylalanine with halogenated nucleosides [116,117]. Surprisingly, use of protected nucleosides in combination with Pd(OAc)₂ and JohnPhos in dioxane proved to be ineffective. However, when the water-soluble TPPTS ligand was employed with unprotected 8-bromo-adenine nucleosides and 4-boronophenylalanine, efficient cross-couplings followed. These reactions were facilitated by microwave irradiation at 150 °C for 5 min, yielding the desired compounds in excellent optical purity, as determined by FDAA analysis [116]. Following these results, Čapek and coworkers also successfully coupled 6- or 8-halogenated purine nucleosides with 4-BPA in the presence of TPPTS and Pd(OAc)₂ [117]. In addition to pinacol esters, the MIDA boronate group was also introduced on aromatic amino acids such as **49** by Colgin et al. [114]. Starting from compounds **47** and **48**, a Negishi coupling and subsequent Suzuki–Miyaura reaction yielded **50** in mixed aqueous conditions (dioxane/H₂O 10:1) with Pd(OAc)₂ as the precatalyst and SPhos as ligand (Figure 9B). Very recently, Bartocinni showed that racemic (7-pinacolborono)tryptophan **51** can be transformed to biaryl products **52** via Suzuki–Miyaura reaction in mixed aqueous conditions (Figure 9C) [118]. Similarly, access to (7-pinacolborono)tryptophan via selective Ir-catalysis allowed Loach to prepare arylated tryptophan derivatives [119]. Meyer et al. reported the selective borylation of phenylalanine (in the presence of a directing group, for example Cl on the 3-position) and heteroaromatic amino acids, such as 2-thienylalanine, 3-pyridinylalanine, and tryptophan [111]. To show the applicability of their methodology, protected borylated thienylalanine **54** was converted to **55** (Figure 9D). When comparing the optimized reaction conditions found for the derivatization of arylboronate esters with conditions commonly applied for the Suzuki–Miyaura reaction of halogenated amino acids and peptides, one can conclude that in the former case higher reaction temperatures and/or prolonged reaction times are often required. In addition, the limited stability of pinacolyl boronate esters towards conditions commonly applied during solid-phase peptide synthesis requires careful design of the peptide assembly [120]. Although the use of other protected alkylboronic acid analogues may circumvent this problem, as exemplified via MIDA-boronates [114], the pinacol ester functionality is used in most cases.

In contrast to the absence of Suzuki–Miyaura reactions involving amino acid-based alkyl halides, the synthesis and derivatization of borylated aliphatic amino acids have been described extensively. These have been prepared via hydroboration of protected allylglycine [121–125], quenching of a lithiated serine analogue with triisopropylborate [126], a Cu-catalyzed cross-coupling of *gem*-diborylalkanes with primary alkyl halides [127], and very recently by Pd-catalyzed C(sp³)-H bond activation (selected examples are shown in Figure 10, left side) [128].

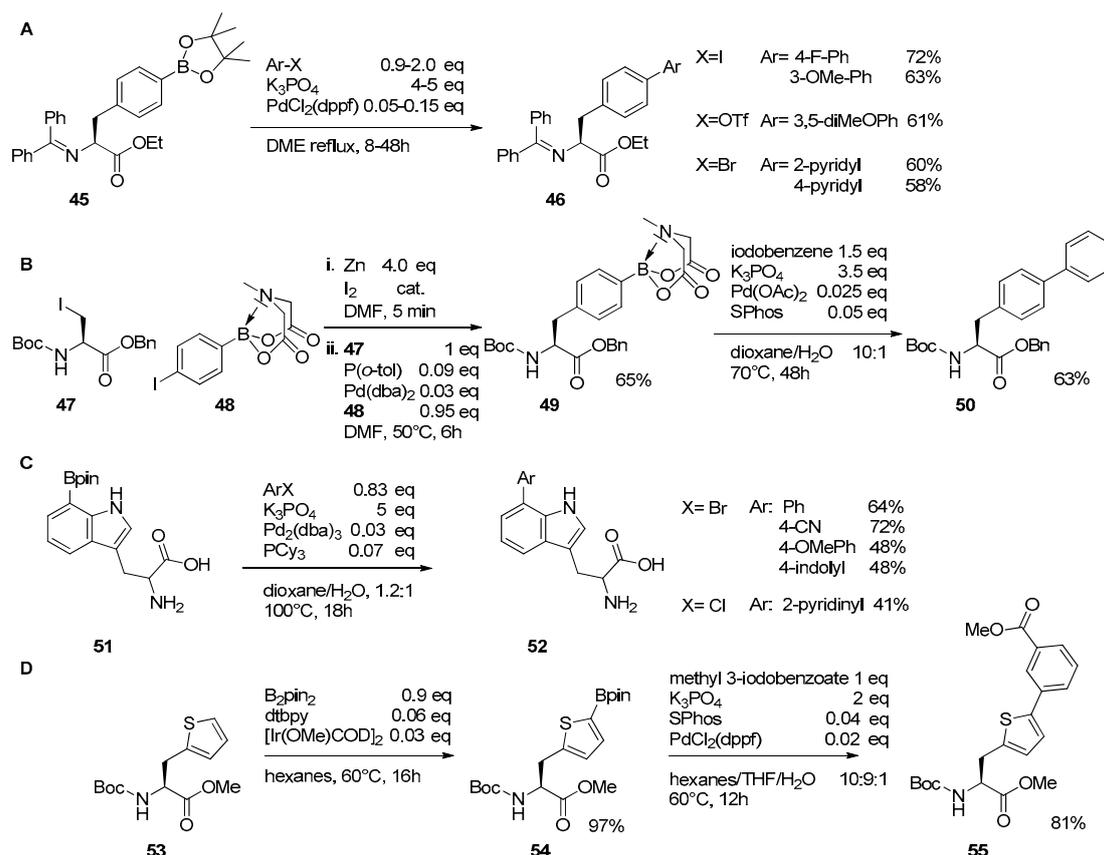


Figure 9. (A) Derivatization of *N*-benzophenone protected pinacolboronophenylalanine **45** with aryl halides. (B) Biphenylalanine **50** synthesis from the corresponding MIDA-boronate **49**. (C) Preparation of racemic 7-aryltryptophan **52** by Suzuki–Miyaura reaction of the unprotected pinacolborono-*D/L*-tryptophan **51**. (D) Protected thienylalanine **53** transformed to biaryl **55** via subsequent Ir-catalyzed borylation and Suzuki–Miyaura cross-coupling.

Campbell prepared bishomophenylalanine derivatives **58** by hydroboration of protected allylated oxazolidine **56** with 9-borabicyclo[3,3,1]nonane (9-BBN), followed by Suzuki–Miyaura reaction with aryl iodides and phenyl bromide in good yields (Figure 10A) [121]. The homologated phenylalanine analogues were obtained in mediocre yields (30%–50%) after oxidation with Jones' reagent ($\text{CrO}_3/\text{H}_2\text{SO}_4$) (not shown). Comparable work was also published by Sabat, which expanded the scope of the reaction to aryl triflates and heteroaryl bromides as substrates, giving way to oxazolidines like **58** in decent yields [122]. The oxidation protocol was further optimized to obtain the α -amino acid analogues in yields up to 82% with excellent optical purity. Collier et al. further improved the procedure by performing the hydroboration–Suzuki protocol directly on protected allylglycine **59**, yielding bishomophenylalanine derivatives **61** in two steps (Figure 10B) [123]. Extension to higher phenylalanine homologues was achieved by Rodríguez and coworkers [124]. In their work, but-3-enylglycine was prepared via Negishi coupling and after hydroboration, access to higher homologues was realized via Suzuki–Miyaura cross-couplings (not shown). Alternatively, a borylated serine analogue **63** was prepared by Harvey et al. by quenching an organolithium species (derived from **62**) with trisopropylborate. This building block was transformed to non-proteinogenic phenylalanine analogues **64** by Suzuki–Miyaura reaction in the presence of Ag_2O (Figure 10C). The corresponding amino acid was obtained after consecutive 2-(trimethylsilyl)ethoxymethyl (SEM) deprotection and a two-step oxidation with Dess–Martin periodinane and Pinnick oxidation (not shown).

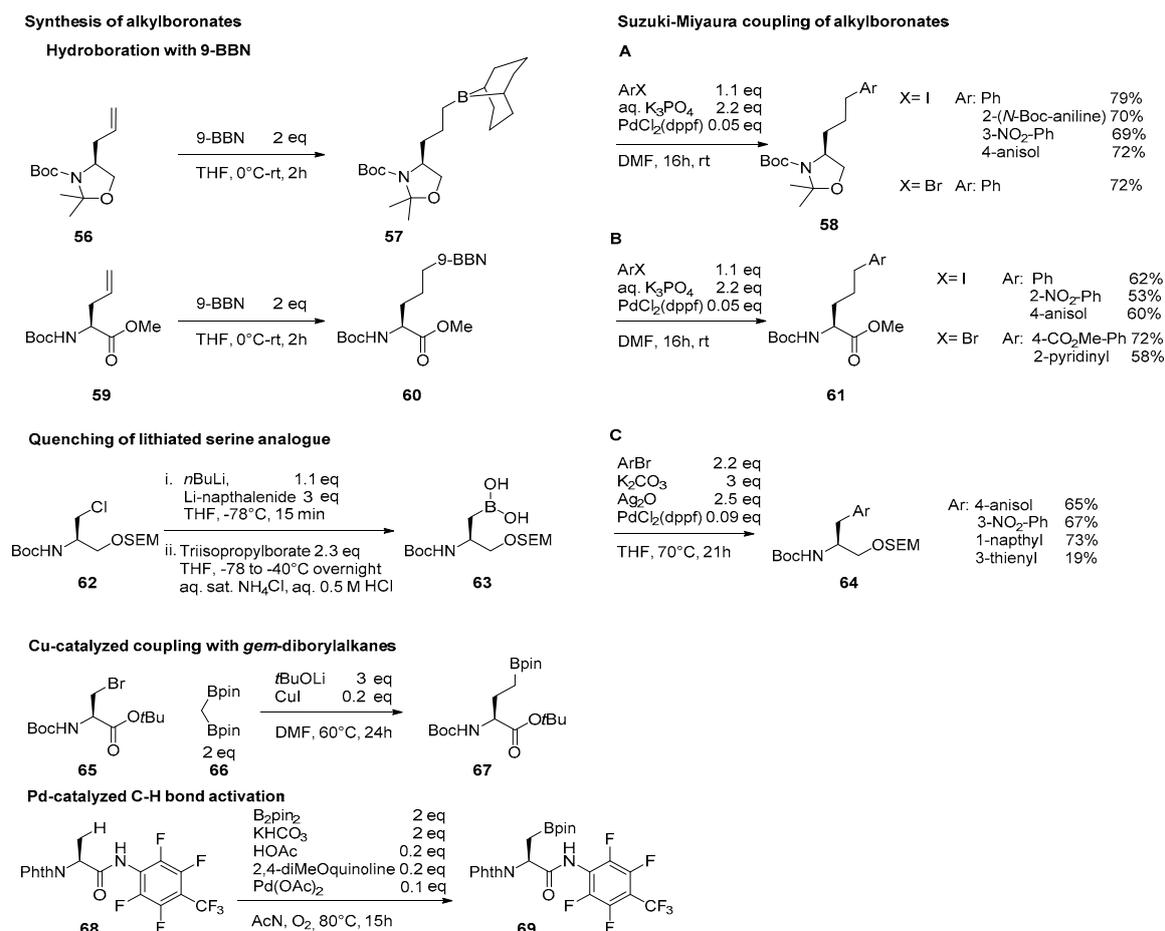


Figure 10. (Left) Representative examples of the preparation of amino acid alkylboronates. (Right) Synthesis of phenylalanine and analogues thereof prepared (A) via hydroboration/Suzuki–Miyaura protocol on protected allylated oxazolidine 56 (B) directly from protected allylglycine 59 or (C) from borylated serine analogue 63.

2.3. Coupling of Amino Acids: Synthesis of Biaryl-Bridged Dipeptides

Yoburn investigated the synthesis of protected dityrosine substrate 70 (Figure 11) [129]. Initially, homocoupling of Ac–Tyr(3-I, 4-OBn)–OMe was performed in a one-pot borylation-Suzuki–Miyaura protocol with PdCl₂(dppf) and B₂pin₂. Here, K₂CO₃ was essential as a base in order to obtain efficient cross-coupling, since use of KOAc only led to borylation of the iodotyrosine educt. Reaction rates and conversions were however significantly lower when the substrate's complexity was increased, for example, to tripeptides. Next, isolation of the borylated peptide intermediate was envisaged and coupling proceeded smoothly when KOAc was used as a base. As such, Suzuki–Miyaura cross-coupling between peptide substrates bearing iodo- and boronotyrosine residues proceeded efficiently, and a viable strategy for homodimerizations (up to heptapeptides) was realized. These findings were simultaneously reported by Hutton et al. [130]. Similarly, Kotha synthesized dimers of protected phenylalanine 71 with racemic 4-boronophenylalanine and 4-iodophenylalanine (Figure 11), along with several unnatural bis-armed amino acids containing a variable number (one to five) of benzene rings [131]. In addition to their investigations on the racemization of phenylglycine under Suzuki–Miyaura conditions [94], Prieto further elaborated on the cross-coupling between 4-hydroxyphenylglycine and tyrosine or tryptophan derived building blocks [132]. Using standard reaction conditions, up to 32% of undesired diastereoisomer was found. Racemization could be suppressed (with up to 99% ee) via usage of the Buchwald ligand SPhos [9], eventually yielding biaryl

building block **72** (Figure 11). Synthesis of these biaryl-bridged building blocks **71–72** represents a basis to obtain cyclic peptides when intramolecular couplings are performed (*vide infra*).

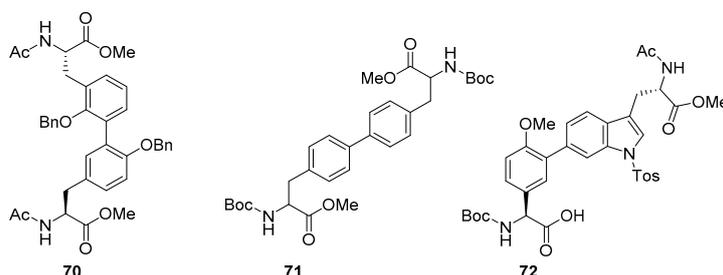


Figure 11. Amino acid homo- and heterodimers **45–47** by intermolecular Suzuki–Miyaura cross-coupling.

2.4. Suzuki–Miyaura Reaction on Peptidic Substrates

Transposition of the Suzuki–Miyaura reaction from amino acid to larger, more complex peptides substrates required adapted methodologies. While solubility of protected amino acid substrates in organic solvents is not an issue, peptide substrates, and by extension proteins, are preferentially treated in aqueous conditions. Circumvention of the traditional solvents (e.g., toluene, DMF, dimethoxyethane) and lower reaction temperatures complicated the envisaged transformations. Moreover, application of the reaction with water as (co-)solvent demands a catalytic system that achieves high conversions in this environment, whilst avoiding side product formation. One needed to move away from the use of $\text{Pd}(\text{PPh}_3)_4$, $\text{Pd}_2(\text{dba})_3$ or $\text{Pd}(\text{OAc})_2$, combined with classical (phosphine) ligands such as the ones used in sections above (Figure 12, compounds **73–76**), and out-of-the-box catalytic systems were required. One solution was found in designing more hydrophilic analogues of traditional ligands [11,62]. For example, 3,3',3''-phosphanetriyltris(benzene sulfonic acid) trisodium salt (TPPTS **77a**, Figure 12) [18,64], its xylene analogue TXPTS **77b** [64,133], sodium 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl-3'-sulfonate (SSPhos **78**) [10,96], and water-soluble NHC-ligands (*N*-heterocyclic carbene), such as **79** [134–137], have been proposed for Pd-catalysis in aqueous media (Figure 12). Suzuki–Miyaura reactions encompassing other water soluble ligands [11,12,138], or additives such as polyethyleneglycol and surfactants were also applied [11,34,139] Notably for Suzuki–Miyaura reaction in aqueous conditions, ligands containing the guanidine functionality, such as 2-aminopyrimidine-4,6-diol disodium salt (ADHP **80a**) [63,140], its dimethylated analogue (*N,N*-diMeADHP **80b**) [34], and (methyl)guanidines **81** and **82** [34,141,142], have been reported.

The development of peptide diversification through Suzuki–Miyaura reactions in a purely aqueous environment was first reported by Vilaró et al. [143]. By combination of $\text{Pd}(\text{OAc})_2$ and the water-soluble sulfonated triphenylphosphine (TPPTS) ligand, couplings were realized in aqueous media on unprotected peptides **83** in very mild conditions (Figure 13A). Nearly quantitative yields were reported starting from the iodinated Leu-enkephalin analogue **83**, bearing neither main chain nor side chain protection. These transformations were realized upon application of potassium aryltrifluoroborates as reactants [7,9]. As expected, it was found that not only the length of the peptide chain, but also its respective amino acid composition were critical. For example, conversions in the presence of a histidine residue were greatly reduced. This can easily be rationalized by a potential complexation of unprotected side chains - but also the main chain termini- with the palladium catalyst, hence interfering with the envisaged derivatizations. During their exploration for phosphine-free catalyst systems, Chalker et al. observed that an aqueous solution of the sodium salt of ADHP **80a** and $\text{Pd}(\text{OAc})_2$ could be used for cross-couplings of partially unprotected substrates like **85** in purely aqueous conditions (Figure 13B) [63]. In addition, mono- and bis-arylations were realized when, respectively, 3-iodotyrosine or 3,5-diiodotyrosine was introduced in the unprotected peptide sequence.

Despite limited catalyst loadings (1–4 mol %), high conversions were obtained for halogenated phenylalanines, tyrosines, and *p*-iodobenzyl cysteine (Pic, such as in **85**). In contrast, in case of reactions on chlorophenylalanine- or substrates bearing Cys (unprotected in the side chain), these derivatization reactions were unsuccessful, presumably, due to the fact that the palladium catalyst is not electron-rich enough. Extension of their work showed that both the dimethyl analogue of ADHP (i.e., Me₂ADHP **80b**) and methylated guanidine **81** or **82** outperformed the ADHP catalyst system when a complex PEG-bound phenylboronic acid was utilized [34]. The latter consisted of monomethoxy-PEG (MW 2 k or 20 kDa) linked to 4-propylcarbamoylephenylboronic acid.

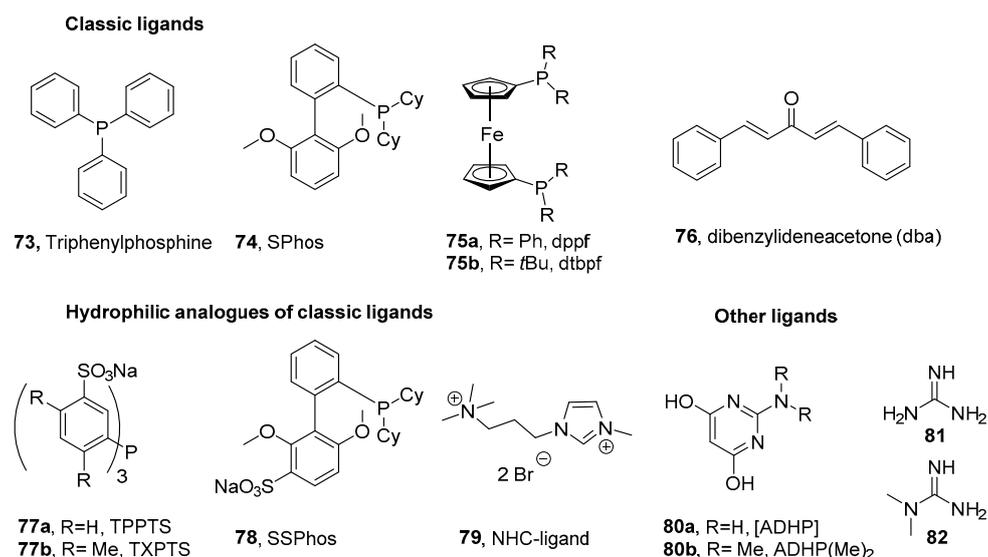


Figure 12. Ligands used Suzuki–Miyaura cross-coupling reactions on peptides. Classical ligands (**73–76**) that have commonly been used in the early developments on protected peptide substrates. Hydrophilic analogues (**77–79**) and non-classical ligands (**80–82**) used in aqueous media.

In order to unravel side/main chain functionality that hampers the application of Suzuki–Miyaura conversions on peptides, Willemse et al. performed a systematic screening of unprotected peptide main and side chain functionalities with various aqueous soluble ligands on dipeptide substrates of type **87** (Figure 13C) [97]. It was shown that, in purely aqueous conditions, a precatalyst solution of ADHP and Pd(OAc)₂ led to efficient derivatizations of dipeptides containing 4-bromophenylalanine. Presence of histidine, bearing an imidazole moiety, and asparagine, bearing a primary amide, were revealed to be troublesome during the targeted cross-couplings. Alteration of the catalytic system to the ferrocene-containing catalyst PdCl₂(dppf) resulted in improved conversions in these cases. However, in order to achieve solubility of the catalyst and efficient cross-couplings, a water/*i*PrOH mixture was required. For the investigated histidine-containing peptides, maximum conversions of approximately 50% were reached, despite efforts to pre-saturate the imidazole moiety by the addition of sacrificial Lewis acids (e.g., MgCl₂) prior to the cross-coupling, as was previously successfully reported for ring-closing metatheses (RCM) and Heck reactions [82,144,145]. Derivatizations on a large peptide (**89**, 34 amino acid residues) in aqueous conditions were performed by Ojida et al. [146] (Figure 13D). Synthetic analogues of the WW domain (6–39) of PinI protein were prepared via SPPS assembly of a peptide containing an iodophenylalanine residue and subsequent Suzuki–Miyaura reactions. Experiments indicated that the addition of glycerol (10% v/v), known to stabilize proteins, to a Tris-HCl buffer (pH 8) was mandatory to reach high yields. Remarkably, the reaction temperature could be limited to 40 °C when using 1 equivalent of Na₂PdCl₄.

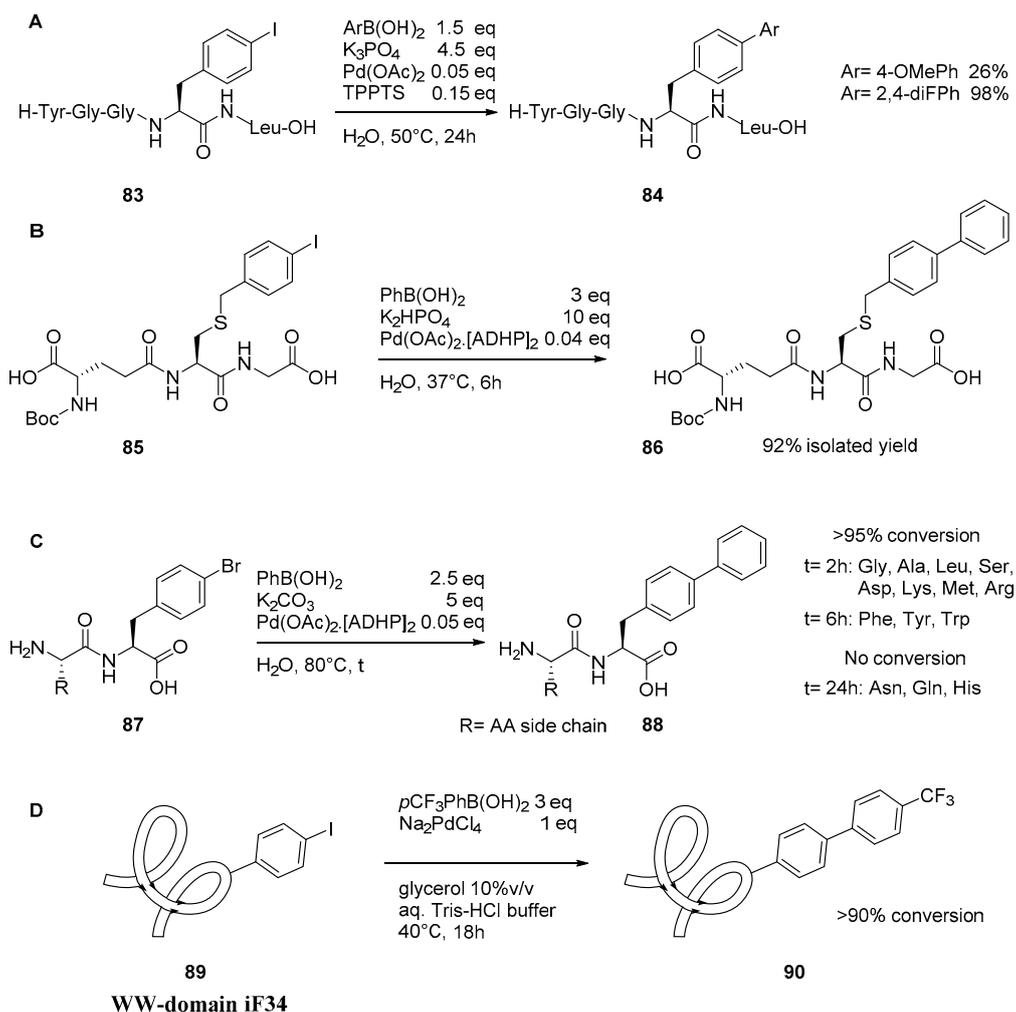


Figure 13. Suzuki–Miyaura reactions on peptides (A) Unprotected pentapeptide **83** as a substrate. (B) Internal *p*-iodobenzylcysteine residue transformed to biaryl tripeptide **86**. (C) Use of unprotected dipeptides **87**. (D) Derivatization of 34-mer **90**.

3. Solid-Phase Derivatizations of Peptide Substrates

Alternatively to Pd-catalyzed cross-couplings in solution, the derivatization of solid supported substrates offers advantages such as convenient washing steps and easy removal of any excess or unreacted reagents and reactants through filtrations [147,148]. For these cross-couplings on resin, the solvent is of high importance, as it is related to the swelling properties of the solid support. Typically, polystyrene-based resins are used for solid-phase peptide synthesis (SPPS) in organic media (e.g., DMF, CH₂Cl₂), whereas very limited swelling is observed in aqueous conditions or upon use of polar solvents. Alternatively, PS-PEG copolymer resins have been developed to improve swelling in mixed aqueous or polar conditions [149–151]. Of relevance to the current review, the preparation of a solid supported phenylalanine scaffold was first performed by Colombo [152]. Herein, it was shown that the Suzuki–Miyaura reaction of 4-iodophenylalanine anchored on Rink Amide resin was possible by means of biphasic conditions (EtOH/toluene 7:3), Pd(PPh₃)₄ precatalyst, and an aqueous solution of Na₂CO₃, albeit full conversion was not reached in these reactions. In their work, Wang resin was the first to be evaluated as the solid support; however, under the applied conditions, significant loss of product because of benzyl ester hydrolysis (i.e., linkage between amino acid and support), and low purity was observed. Performing the reaction on Rink Amide resin afforded desirable transformations. Limbach et al. reported Suzuki–Miyaura reactions on a Rink

Amide resin linked pentapeptide containing a brominated β^3 -homophenylalanine [91]. In their hands, $\text{Pd}(\text{PPh}_3)_4$ and Na_2CO_3 in a mixture of $\text{EtOH}/\text{toluene}/\text{H}_2\text{O}$ solvent system resulted in high conversion. The “on support” derivatization was further elaborated by Nielsen et al. on hydroxymethylbenzoic acid-polyethylene glycol (HMBA-PEG) resin (Figure 14A) [153]. Peptide substrates anchored on this base-labile resin and containing either a 3- or 4-iodophenylalanine residue were derivatized to yield Compound 92 after coupling with a variety of arylboronic acids, K_3PO_4 and $\text{PdCl}_2(\text{dppf})$ in a biphasic ($t\text{BuOH}/\text{toluene}/\text{H}_2\text{O}$) medium.

Similarly, Le Quement and co-workers reported the solid-phase derivatization of thienylalanine containing peptides 93 (Figure 14B) on HMBA-PEG₈₀₀ resin [154]. By solid-phase peptide synthesis, the 3-thienylalanine residue was introduced and subjected to Pictet–Spengler cyclization and bromination, to obtain 94 on support. From this compound, a set of cross-coupled products 95 could be obtained in good yields. Under analogous conditions, a derivatization strategy was employed to access biaryl pentapeptides with antagonistic effect on inhibitors of apoptotic proteins [155]. Additionally, a library of antimicrobial peptides was prepared by Haug et al. via the Suzuki–Miyaura reaction on tripeptides containing 4-iodophenylalanine [156]. Here, a Rink Amide linker on NovaGel resin (i.e., a PS-PEG resin) was employed as the solid support for the preparation of the Boc–Arg(Pbf)–Phe(4-I)–Arg(Pbf)–Rink amide educt. Successful cross-couplings with different bulky arylboronic acids were realized with $\text{Pd}(\text{OAc})_2$ and $\text{P}(o\text{-tolyl})_3$ as the catalyst system in mixed $\text{DME}/\text{H}_2\text{O}$ (not shown).

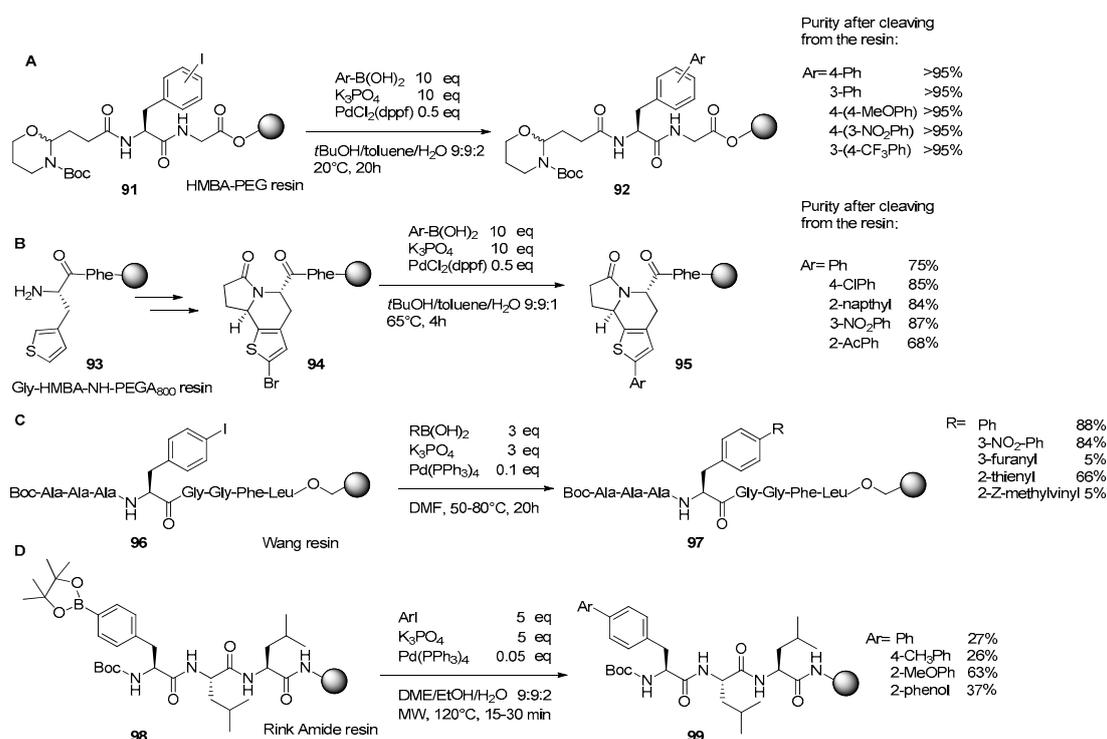


Figure 14. Solid-Phase derivatization via Suzuki–Miyaura cross-coupling (A) with iodophenylalanine containing 91, (B) with bromothierylalanine containing 94, (C) with 4-iodophenylalanine containing octapeptide 96, and (D) with tripeptide 98 bearing pinacol protected 4-borono-L-phenylalanine.

Doan et al. reported the solid-phase derivatization of an enkephalin-like octapeptide sequence 96 (Figure 14C) [157]. The peptide, prepared on Wang resin, was modified using a variety of bases, solvents, catalysts and temperatures. Based on earlier reports on the instability of resin-bound peptides with unprotected *N*-termini [153], the final amino acid was introduced with a Boc protecting group. In their hands, aqueous solutions of weak bases (K_3PO_4 or Na_2CO_3) in combination with DMF as solvent proved to be optimal. It was also found that the use of $\text{Pd}(\text{PPh}_3)_4$ as catalyst at a maximum

temperature of 80 °C for 20 h provided access to a range of biaryl containing peptides **97**. Not surprisingly, low yields were obtained upon insertion of several heteroaryl moieties, and significant side products were formed upon prolonged exposure to high temperature (>100 °C).

Interestingly, Afonso et al. disclosed for the first time the preparation of biaryl-containing peptides from 4-iodophenylalanine by sequential solid-phase borylation and Suzuki–Miyaura conversion [158]. Their approach relied on the introduction of the arylboron group by Miyaura borylation on Rink Amide resin. Treatment of polymer-bound halogenated peptide with the optimized catalytic conditions, being B₂pin₂/KOAc/PdCl₂(dppf) in DMSO, afforded the boronopeptidyl resin **98** (Figure 14D) with excellent conversion, as determined by HPLC after small scale cleavage. Next, the cross-coupling was investigated with iodobenzene in degassed DMF under microwave irradiation. Initially, only minor conversions were attained, and side products, including deborylated or homocoupled peptide, were formed. By switching the solvent system to DME/EtOH/H₂O 9:9:2, in combination with the use of an aqueous solution of K₃PO₄, improved reaction efficiency was obtained, and gratifyingly, target arylated peptides **99** were accessed in acceptable isolated yields. In an extension of their work in solution phase [93], Cerezo reported the first solid-phase derivatization of 5-bromohistidine containing tripeptides (not shown) [159]. The 5-bromo-histidine residue was introduced as the *N*-terminal amino acid via SPPS on Rink MBHA resin and subjected to Suzuki–Miyaura reactions. The imidazole moiety was protected with a SEM-group (as in Figure 5B). In comparison with their optimal solution-phase conditions, elevated temperatures (170 °C) and a solvent change to DME/H₂O/MeOH was required.

4. Formation of Biaryl-Bridges in Peptidic Natural Products and Peptide Macrocyclics

By introduction of halogen and boron groups onto amino acid side chains, the preparation of biaryl products starting from two amino acids can be envisaged (see Section 2.3). First reports of these biaryl linkages in cyclic structures via Suzuki–Miyaura reactions were inspired on peptidic natural molecules such as complestatin. Elder and coworkers synthesized a model ring system **105** based on complestatin [160]. In their work, two syntheses are reported, going either via intramolecular cross-coupling of **103**, containing brominated tryptophan and borylated tyrosine residues (Figure 15A) or via lactamization of a biaryl-bridged intermediate **104**. The *D*-tryptophan residue in **103** and **104** was prepared via a key enantioselective ene-reaction between **100** and **101** with (*S*)-(-)-2,2'-*p*-tolyl-phosphino)-1,1'-binaphthyl ((*S*)-Tol-BINAP). The unnatural protected amino acid **102** was obtained in excellent ee (94%). After peptide assembly in solution, **103** was submitted to Suzuki–Miyaura coupling condition (Figure 15A, reaction parameters not fully disclosed). Alternatively, the 17-membered ring system in **105** could be formed by activation of **104** with pentafluorophenyl diphenylphosphinate (FDPP) in diluted DMF.

The synthesis of biphenomycin analogue **107** was reported by Carbone et al. Instead of isolating the pinacolatoboron intermediate, the diiodinated ortho-substituted Compound **106** was converted to biaryl **107** in a tandem procedure with B₂pin₂ and PdCl₂(dppf) (Figure 15B) [161]. The efficiency of such a tandem reaction was, however, moderate and highly dependent on the concentration of the reaction, with significant formation of de-iodinated compound. The interest of the Zhu group in the use of Suzuki–Miyaura reactions for natural product synthesis was further illustrated by the synthesis of RP-66453 **108** [162], and the concise asymmetric total synthesis of biphenomycin B, wherein this cross-coupling served as the final step [107]. A different approach was reported by Waldmann et al. [163]. Here, the biaryl bridge in **108** was first prepared via intermolecular Suzuki–Miyaura of a pinacolatoboron- and iodo-precursor. The cyclization was then performed by lactamization, to again provide **108**. Owing to their widespread occurrence in nature [61] and the efficient access of biaryl-bridged peptides via Suzuki–Miyaura cross-couplings, multiple research teams focused their efforts on natural product synthesis of, among others, TMC-95A/B **109a,b** [164–168], arylomycins **110a,b** [169], complestatin [170,171] and Rubiyunnanin B [172], wherein the Suzuki–Miyaura reaction often serves as the disconnection site of the biaryl-bridge (Figure 15C).

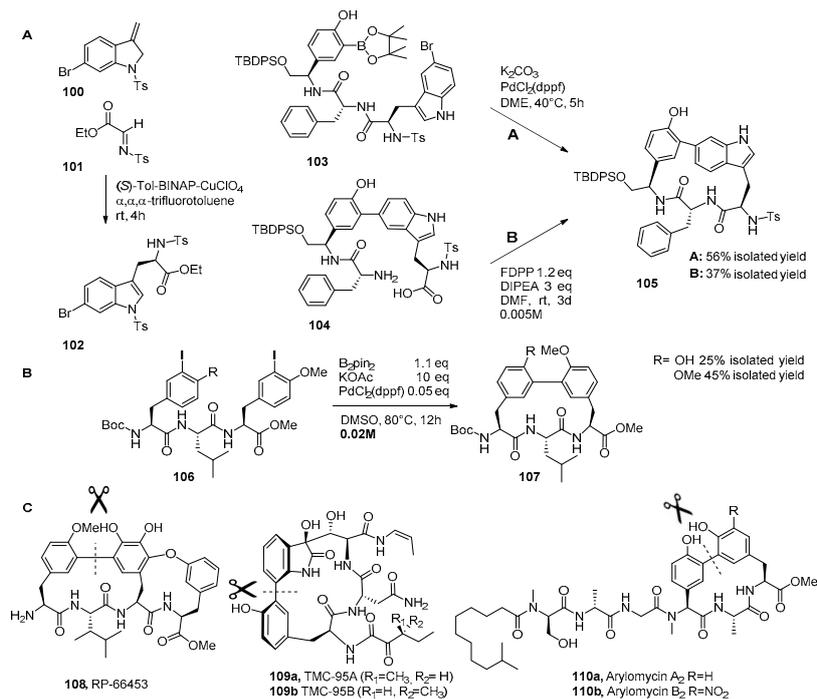


Figure 15. Cyclic peptide synthesis via Suzuki–Miyaura reactions. (A) Synthesis of a part of the ring system of complestatin (B), **105**. One-pot borylation - Suzuki–Miyaura on diiodinated substrate **106**. (C) Disconnection strategy for different natural products **108–110**, bearing a biaryl bridge.

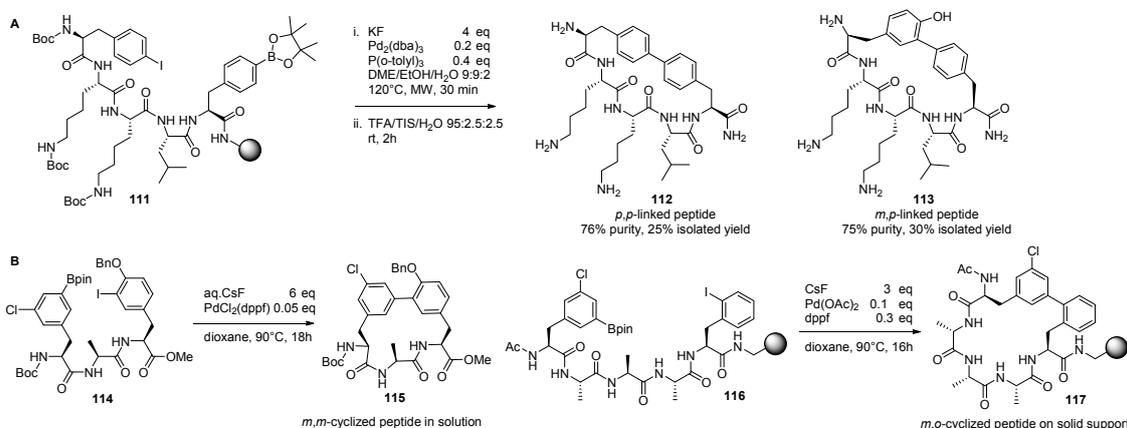


Figure 16. (A) Solid-phase synthesis of biaryl-linked peptide **112** with *p,p*-motif and **113** with *m,p*-motif. (B) Synthesis of *m,m*- and *m,o*-cyclic peptide **115** and **117** via respective solution-phase and solid-phase Suzuki–Miyaura.

Afonso et al. extended their work on cross-couplings of borylated peptides on solid support [158] through the cyclization of a linear peptide, for example, **111**, containing both the boronate and the halogenated aromatic amino acid [120]. Different ring sizes were obtained by varying both the length of the peptide sequence (three to eight residues) and the position of the halogen atom on the *N*-terminal amino acid (*p*-I-Phe, *m*-I-Tyr and 3-Br-His). The cyclization was carried out under microwave conditions and provided the expected biaryl cyclic peptides in high purity for both *p,p* and *m,p*-linked peptides as exemplified by, respectively, **112** and **113** in Figure 16A. An extension to their study was performed by alteration of the borylated residue [173]. The peptidyl resin containing protected 3-iodotyrosine was first borylated; and, after extension of the peptide chain, either protected 4-iodophenylalanine or 3-iodotyrosine was added to synthesize the *p,m*- and *m,m*-crosslinked biaryl

peptides (not shown). Meyer et al. report the preparation of additional combinations of biaryl-bridged peptides [174]. Either a solid- or solution-phase approach allowed *m,m*-, *o,m*-, and *m,o*-bridged cyclic peptides, for example, **115** and **117**, through regiochemical variation of the aryl halide and arylboronate (Figure 16B). While solution-phase couplings were reported with PdCl₂(dppf) precatalyst, the solid-phase reactions were performed with Pd(OAc)₂ and dppf.

5. Protein Derivatization

Substrate complexity was pushed further and proteins bearing halogenated or borylated amino acid side chains were considered. Labeling of protein substrates through natural amino acid side chains is commonly carried out on cysteine, lysine or even aspartic acid side chains [31,175]. However, the abundance of nucleophilic groups in proteins hampers site-specific alteration of the substrates and emphasized the necessity for a chemoselective reaction toolbox. For this purpose, chemoselective bioorthogonal reactions have been explored and exploited for labeling substrates such as peptides and proteins, but these conversions have also been used for other purposes, namely to change the pharmacokinetic and pharmacodynamic properties of biologically relevant peptides and proteins [29–33]. Popular bioorthogonal reactions examples include the Staudinger ligation, click chemistry, cycloadditions, and transition-metal catalyzed C–C bond formation. Of interest to this work, the potential of palladium-mediated chemistry has even been extended to living cells [176–178]. However, in case of transformations on highly complex proteins, containing multiple complexation sites, superstoichiometrical quantities (often palladium >50 eq, boronic acid >500 eq) are required. Since the allowed palladium level thresholds in active pharmaceutical ingredients are very low and metal impurities can affect activity and toxicity studies of the target compounds, analysis and removal of palladium impurities is of utmost importance [179]. Due to the scale of all described reactions (R&D phase), recycling of the precious metal catalysts has not been studied in much detail when working on protein substrates. An exception to this can be found in the work of Dumas, which shows that inductively coupled plasma (ICP) with optical emission spectrometry (OES) can provide quantitative data on palladium content in protein samples after Suzuki–Miyaura reaction [34]. The addition of 3-mercaptopropionic acid has been shown to efficiently remove palladium from the protein surface [180]. Furthermore, recoverable palladium nanoparticles have been shown to possess excellent catalytic activity for the transformation of brominated or iodinated amino acids [145]. However, in view of future upscaling efforts, recyclability will have a major impact on newly developed methodologies [179,181]. Recent reviews on sustainable Suzuki–Miyaura reactions in aqueous media discuss the use of recoverable catalysts, yet these are limited to non-peptidic substrates [11,138,182]. In this respect, several recyclable catalysts [183–190], including silica- or polymer-supported catalysts and magnetically recoverable catalysts, are reported for biaryl formation and could potentially be implemented for transformations of peptide substrates.

Site-specific carbon–carbon bond formation on proteins was first realized by Kodama through Mizoroki–Heck and Sonogashira reactions on a His₆-fused Ras protein containing a 4-iodophenylalanine residue (iF32-Ras-His) [65,82]. The first example of a Suzuki–Miyaura reaction on protein substrates was reported by Brustad and coworkers via expansion of the genetic code, which allowed selective introduction of a 4-boronophenylalanine residue [83]. Subsequently, the Suzuki–Miyaura reaction induced the coupling of a fluorescent iodoaryl boron-dipyromethene (bodipy-I) scaffold through use of Pd₂(dba)₃ complex in an aqueous buffered solution (20 mM EPPS) at 70 °C, though in a moderate conversion (ca. 30%) (Figure 17A). Both bodipy-I and Pd₂(dba)₃ were added in 20-fold excess with respect to the borylated protein. Chalker et al. previously showed that an aqueous catalyst solution of the sodium salt of 2-amino-4,6-dihydropyrimidine (ADHP, **80a**) and Pd(OAc)₂ catalyzed cross-couplings in excellent yields on C-terminally unprotected amino acids using only buffered aqueous conditions at 37 °C (vide supra, Section 2.4) [63]. Their elegant method was extended towards protein-based substrates by introduction of *p*-iodobenzyl cysteine (Pic) as replacement of a single cysteine residue in a subtilisin *Bacillus lentus* (SBL) mutant S156C

(SBL-156ArI, Figure 17B) [63]. To ensure fast couplings, an excess of the catalyst solution (50 eq) and boronic acid (500 eq) were employed. Further research by the Davis group also showed that when 4-iodophenylalanine is present in a His₆-tagged maltose binding protein (MBP), the ADHP-Pd(OAc)₂ combination was again perfectly suited for the envisaged derivatization [180]. Similarly, 50 eq of palladium catalyst and 680 eq of boronic acid were required for achieving complete conversion after 2 h at 37 °C. Reaction follow-up by mass spectrometry was however hampered by non-specific metal binding to the protein. Therefore, the addition of 3-mercaptopropionic acid scavenger was mandatory to remove palladium and re-emergence of proteinogenic ionic species during MS reaction analysis. Spicer et al. expanded the scope of the Suzuki–Miyaura reaction to living cell surface proteins [191]. Four mutant plasmids of the OmpC protein were co-transformed into *E. coli* cells to incorporate 4'-iodo-L-Phe, via amber stop codon suppression, in different loop regions of cell-surface channels. The Pd(OAc)₂.(ADHP)₂ catalyst system proved again appropriate for efficient labeling with fluorescent dyes on the outside of the cell-surface.

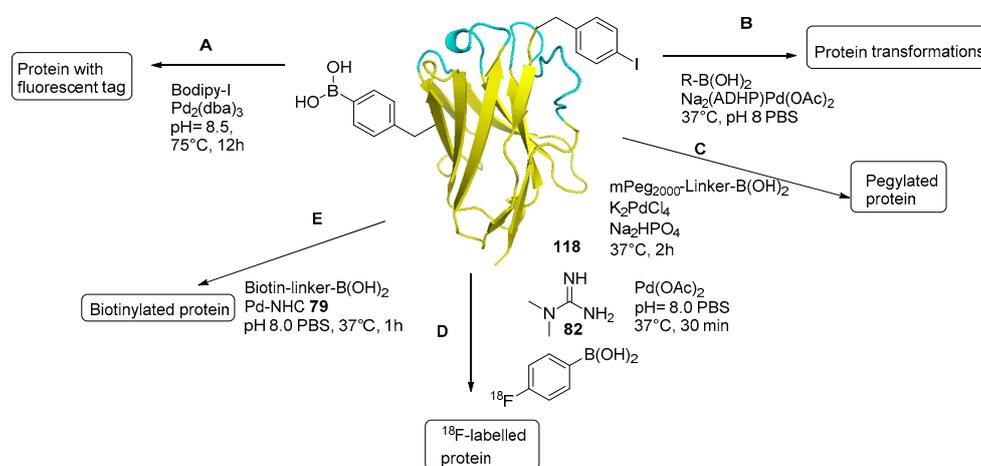


Figure 17. Schematic representation of different strategies for Suzuki–Miyaura reaction on protein substrates. Various proteins were utilized. Here, a common “dummy” substrate **118** is shown for illustrative purposes. (PBS = phosphate buffer).

Attachment of polyethylene glycol (PEG) chain to proteins (also denoted as the “PEGylation” process) is often used to improve stability and pharmacokinetic properties [192]. As a disadvantage, PEG-conjugates cope with a reduced biological activity which is related to the presence of multiple reactive sites at the level of amino acid side chain in the protein (usually lysine or cysteine residues). Therefore, the site-selective PEGylation via Suzuki–Miyaura reactions was envisaged as an alternative approach by Dumas (Figure 17C) [34]. A PEG unit (2 kDa or 20 kDa) was attached to two different iodinated proteins (Npβ-69pIPhe and SBL-156Pic). First, the derivatization of Boc-4-iodophenylalanine was unsuccessfully attempted with a monomethoxy PEG polymer phenylboronic acid (mPEG-PBA) reagent and ADHP as the ligand. Luckily, upon application of structurally related ligands such as 2-(*N,N*)-dimethyl-4,6-dihydroxypyrimidine (*N,N*-diMeADHP) and methylated guanidine derivatives, the derivatizations proceeded smoothly after 2 h at 37 °C. Intriguingly, reaction conversion also proceeded in >90% conversion when no ligand was added to reactions with K₂PdCl₄ as the palladium source. Converting these findings on the iodinated proteins showed that these “self-ligated” conditions resulted in high conversion for both Npβ-69pIPhe and SBL-156Pic with respectively 40 and 10 eq of Pd catalyst and 1000 eq of the mPEG_{2k}-PBA (Figure 17C). Application of the guanidine-based ligands was furthermore explored for the introduction of ¹⁸F tags by Gao et al. [142]. With 1,1-dimethylguanidine **82** as a ligand, the first Pd-catalyzed introduction of ¹⁸F, the most common radionuclide in PET imaging, was exemplified on SBL-156Pic (Figure 17D) with 250 eq of Pd-catalyst solution and 250 eq of labeled 4-fluorophenylboronic acid. Moreover, Ma and coworkers have

shown that water-soluble NHCs, such as **79** (Figure 12), can be applied for protein derivatizations (Figure 17E) [135]. Pd-complexes with NHC-ligands bearing hydrophilic groups were first verified on *N*-Boc-4-iodophenylalanine under mild conditions (37 °C, 2–6 h). The feasibility of this methodology was transferred to a modified Bovine serum albumin (BSA) protein (not shown). In this study, the introduction of the halogen moiety was realized by derivatization of the lysine residues with (*p*-iodophenyl)methyl *p*-nitrophenyl carbonate. Incubation of the iodine-bearing protein *p*IPM-BSA with 100 eq of this Pd-NHC complex and 100 eq of biotin-B(OH)₂ yielded the desired derivatives (Figure 17E). Similarly, a lysozyme containing *p*-iodobenzoate (*p*IBZ-lyso) also underwent efficient cross-coupling with a PEG-bearing boronic acid (not shown) [135]. The utility of this catalytic system was even demonstrated to work on the cell-surface of live mammalian cells. Biotinylation of HeLa cells, pretreated with *N*-succinimidyl *p*-iodobenzoate, was achieved as detected by confocal microscopy. Interestingly, clearly, the high versatility of the Suzuki–Miyaura reaction is demonstrated by successful conversions on the abovementioned and highly challenging substrates.

6. The Suzuki–Miyaura Reaction as a Tool towards Improved Biological Activity

Most of the successful drugs can be subdivided in “small molecules” (MW < 500) and “biologicals” (MW > 5000). The latter class has emerged during the last decades due in part to an improved knowledge of recombinant protein expression and purification. These biomolecules often possess excellent biological activity and selectivity, but they are not amenable to oral bioavailability and come with a high production cost. Up until the past two decades, the large gap between these two classes had been less explored by the pharmaceutical industry. However, peptides of short and intermediate length (<50 AA) lie in the soft spot between small molecules and biologicals [45,193]. They still possess the high specificity for their biological target (which reduces the risk for off-target effects) and they can be made by synthetic organic chemistry. However, if we consider linear peptides bearing natural side chains, several inherent drawbacks arise. When comparing to typical “small molecules,” disadvantages of these small peptides include poor metabolic stability, low (oral) bioavailability, and rapid clearance rates. In this regard, the Suzuki–Miyaura reaction provides a valuable bioorthogonal reaction to the medicinal chemist, as both the introduction of non-natural amino acids and a reduction of side chain flexibility can be realized via this reaction. Biaryl adducts have provided valuable SAR-information and proved to alter the selectivity, stability, and availability of the parent peptide. Selected examples to illustrate this are touched upon below.

The groups of Hagmann and Yang described the optimization of sulfonylated dipeptide inhibitors with subnanomolar inhibitory activity for integrin VLA-4 as illustrated by compound **119**. [194,195]. Highly potent analogues, for example, **120** and **121** (Figure 18A), were obtained when encompassing a biaryllic C-terminal residue. Modification of the substituents on the distal ring of biphenylalanine altered the availability, half-life and clearance rate of the dipeptide ligands. Synthesis of these ligands was carried out by Suzuki–Miyaura reaction on the protected triflated tyrosine [194] or halogenated phenylalanine [195] with Pd(PPh₃)₄ in toluene and the corresponding boronic acids to yield **120** and **121**.

In analogy, dual $\alpha_4\beta_1/\alpha_4\beta_7$ integrin antagonists, for example, **122** and **124**, were designed by Sircar and Castanedo (Figure 18B) [196,197]. Sircar and coworkers prepared ligand **122** via Suzuki–Miyaura-catalyzed cross-coupling of triflated tyrosine or bromophenylalanine with Pd(PPh₃)₄ in DME [196]. Castanedo prepared the ligands via on-resin derivatization with PdCl₂(dppf) in NMP [197]. Exploration of the chemical space surrounding the distal ring of the biphenylalanine moiety indicated that substitution of the ortho-position had a beneficial effect on the inhibitory activity.

Short analogues of Glucagon-like peptide 1 (GLP-1) with potential antidiabetic activity were prepared by Mapelli (Figure 18C) [198]. The natural gastrointestinal peptide hormone exists predominantly as a 30 or 31 amino acid sequence with functional agonist activity at the GLP-1 G protein-coupled receptor. Endogenous GLP-1 is not suitable as a therapeutic agent due to its very short half-life time of ca. 2 min. A lead nonapeptide containing the critical residues for binding was extended

with two biphenyl residues, to yield an 11-mer peptide **125**. The presence of two biphenylalanine moieties was found to be crucial for providing submicromolar agonist activity in the utilized cAMP accumulation assay. Introduction of small substituents on the distal rings of the biphenylalanines further improved the biological activity (EC_{50} decreased to 7 nM, not shown). Additionally, alterations to the initial 9-mer showed a significant improvement in activity (0.087 nM) and resulted in a nearly equipotent analogue **126**, as compared to the endogenous 30-mer, while prolonging the in vivo residence time to 20 h. Introduction of side chain-based macrocyclic constraints by lactam formation as illustrated in **127** or disulfide linkage in **128** produced agonists with stabilized secondary structural motifs (*N*-terminal β -turn and *C*-terminal helix) that differentially influenced affinity and agonist potency [199]. Both Mapelli and Hoang reported the synthesis of the unusual biaryl building blocks via attachment of 4-iodophenylalanine to the solid-support, followed by Suzuki–Miyaura reaction with the respective boronic acids and $Pd(PPh_3)_4$ or $Pd(OAc)_2$ and JohnPhos.

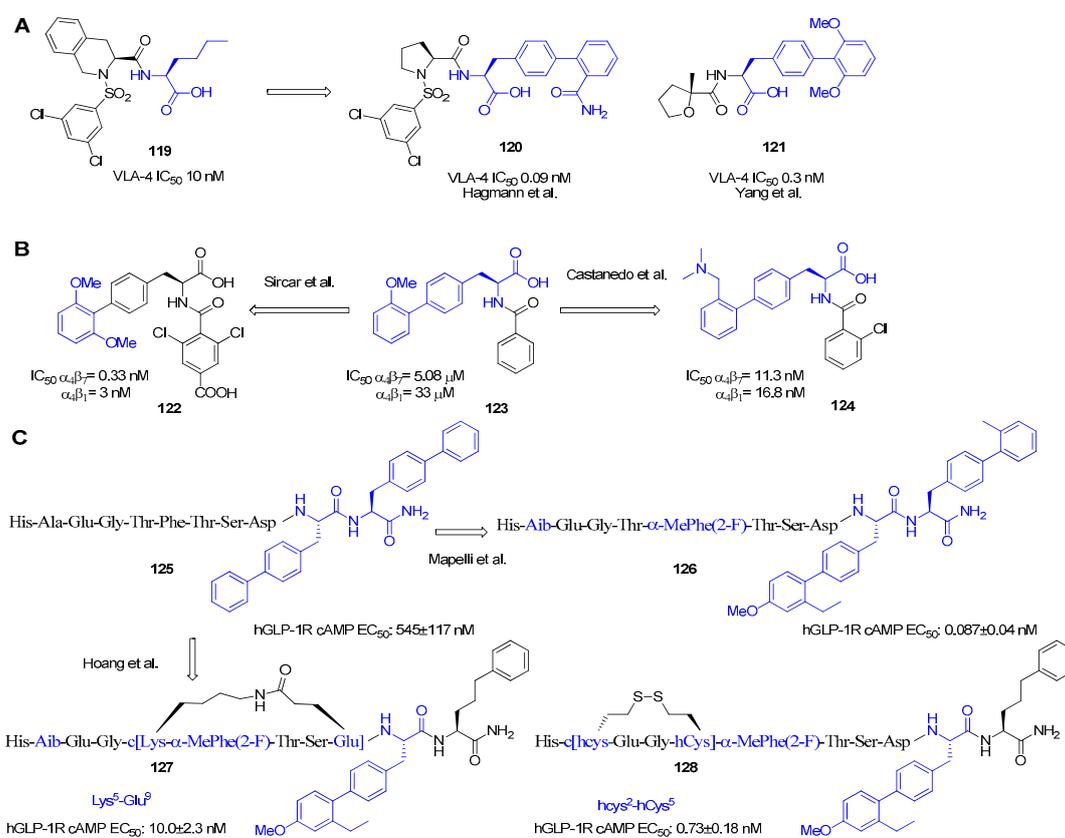


Figure 18. (A) Synthesis of dipeptide ligands **120** and **121** with inhibitory activity for integrin VLA-4. (B) Dual $\alpha_4\beta_1/\alpha_4\beta_7$ integrin antagonists **122** and **124**. (C) Short GLP-1 analogues **126**–**128** that are improved by amino acid substitution (**126**) and introduction of secondary motifs by backbone cyclization (**127** and **128**).

Cationic antimicrobial peptides (CAP) have been studied as a therapeutic alternative to the widespread bacterial resistance of common antibiotics. Typically, the sequences of these amphipathic peptides alternate between cationic residues and hydrophobic moieties. The positive influence of bulky hydrophobic groups has been described in these CAPs [200]. Evidently, biaryl containing peptides **129** and **130** were explored for their activity versus Gram-positive drug-resistance pathogenic bacteria (Figure 19A) [156,201]. In view of the development of novel antimicrobial peptides, Ng-Choi et al. incorporated 5-bromohistidine as a replacement of phenylalanine in undecapeptides at the 1- or 4-position (for example, **131**, Figure 19B) [202]. Derivatization of these building blocks was previously reported on solid-phase [159] and afforded a small library of biaryl peptides, which were

tested for their biological activity in comparison with the lead peptide H-FKLFKKILKFL-NH₂. These arylhistidine-containing peptides displayed similar antibacterial and antifungal activity; however, a decreased hemolytic effect was observed. Hemolysis represents an important concern when developing CAPs.

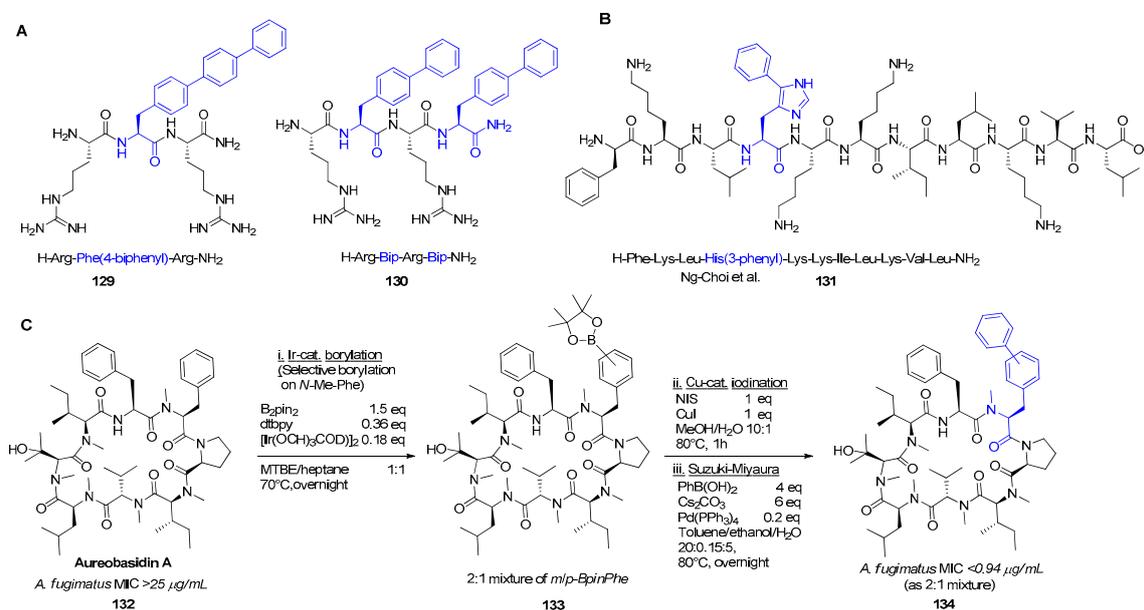


Figure 19. (A) Short cationic antimicrobial peptides **129** and **130** featuring, respectively, triaryl- and biarylphenylalanine (B) Improvement of the antimicrobial activity of undecapeptides by incorporation of 5-arylhistidine (C) Improvement of antifungal activity via borylation-Suzuki–Miyaura reaction on Aurebasidin A **134**.

The Suzuki–Miyaura reaction has also proven useful in the optimization of cyclic peptides. Wuts et al. explored analogues of Aurebasidin A (AbA) as antifungal agent to improve potency against a human pathogen (*Aspergillus fumigatus*) [203]. Selective borylation of the *N*-Me-Phe residue of **132** generated a 2:1 mixture of *m*- and *p*-substituted phenylalanine that was converted to iodophenylalanine and submitted to Suzuki–Miyaura catalysis (Figure 19C). Substrate **134** was found to be a potent ligand with an enhanced minimal inhibitory concentration (MIC) value, as compared to the native AbA.

7. Conclusions

In this review, we covered the initial developments of Suzuki–Miyaura cross-couplings on single amino acids in organic(/aqueous) media up to aqueous reaction conditions for the efficient derivatization of complex protein substrates. A plethora of unusual biaryl substituted amino acids was made accessible through this reaction, starting from either halogenated or borylated residues. Initial work was primarily focused on organic media with typical catalysts (Pd(PPh₃)₄, Pd(OAc)₂, Pd₂(dba)₃), to provide protected amino acids. Progress towards (pre)catalysts that are active, stable and more soluble in aqueous environments and subjected to mild conditions enabled the derivatization of more complex substrates. Especially, water-soluble pyrimidine ligands and hydrophilic analogues of classic ligands (PPh₃, NHCs, SPhos) have made transformations in aqueous media possible. This allowed the late-stage derivatization of peptides, both in solution- and solid-phase, for multiple applications, such as drug discovery and labeling efforts. Furthermore, the constrained biaryl-bridge motif was introduced in peptidic natural products and peptide substrates, and led to cyclic analogues. Transformations on protein substrates were realized as well, albeit superstoichiometrical quantities are required for derivatization of these highly complex substrates. Interestingly, recyclability of the palladium catalysts or recoverability of palladium is typically not discussed yet, due to the small

scale on which the cross-couplings have been executed. Furthermore, catalyst development is still required to achieve higher substrate compatibility and a more broadly applicable catalyst system. Current limitations include the incompatibility of cross-couplings with alkylboronic acids and the limited use of chlorinated substrates. Nevertheless, it is clear that the Suzuki–Miyaura reaction is a powerful tool for the bioorthogonal transformation of amino acid substrates, peptides, and proteins. The incorporation of biaryl-bridged amino acids has been shown to significantly impact the biological activity of peptide sequences, and further development in the field of Suzuki–Miyaura catalysis will definitely have a positive impact on both synthetic methodology and pharmaceutical applications.

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