SYNTHESIS OF MODIFIED TRYPTOPHAN DERIVATIVES

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Abstract. *Numerous natural products contain substituted tryptophans or are derivatives thereof. The syntheses of these heterocyclic amino acids are however not always trivial. Several approaches have been described so far. Some use C–C-bond formation reactions to couple indole units to the amino acid backbone, whereas other methods construct the indole moiety in the side chain of a suitably functionalized amino acid or peptide or introduce substituents by C–H activation of tryptophan. In this chapter, we focus on recent advances in the synthesis of tryptophan derivatives.*

Contents

1. Introduction

Tryptophan (Trp) as one of the 20 proteinogenic amino acids plays a major role in the construction of peptides, signal transduction and metabolism.[1] Furthermore, numerous natural products, especially peptides and indole alkaloids, are derivatives of Trp and often exhibit interesting biological activities.[2-4] These secondary metabolites often show unusual substitutions of the indole moiety, which is sometimes incorporated into complex ring systems.

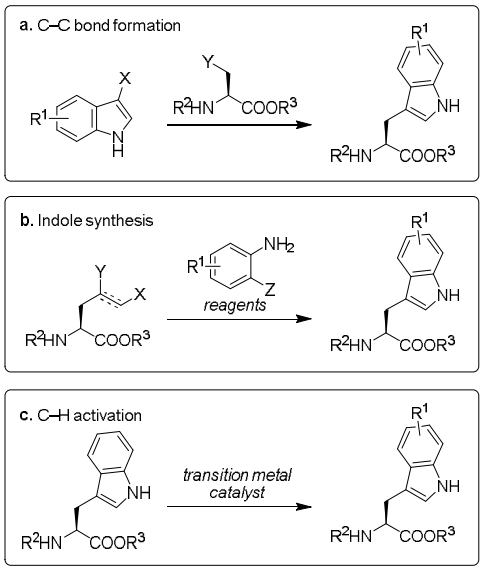
The introduction of substituents on the indole moiety of Trps is not a trivial task. A direct substitution with electrophiles is only possible in 2- or 5-position.[5] To get truly modular access to diversely substituted Trps, the construction from appropriate precursors is therefore required. This can either be accomplished by coupling appropriately substituted indoles to an amino acid precursor (Scheme 1a), or by synthesizing the heterocyclic ring system in the side chain of an amino acid (or peptide) (Scheme 1b). Another approach introduces substituents by selective activation of C–H bonds on Trp using transition metal catalysis (Scheme 1c). In this chapter, we would like to give an overview of the recent methods which have been used to synthesize complex Trp derivatives.

2. Coupling of indoles to the amino acid backbone *via* C–C bond formation

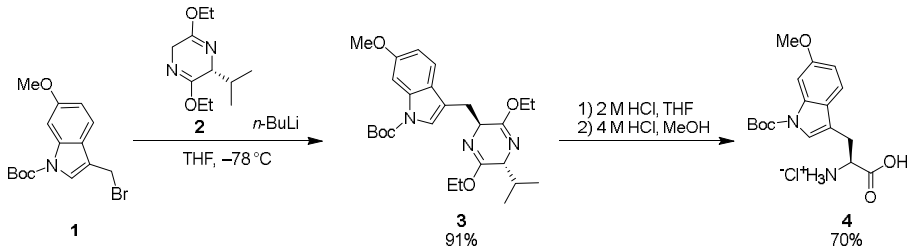
2.1. Alkylation of chiral auxiliaries

Towards the end of the 20th century, the so-called Schöllkopf method was one of the preferred approaches for constructing unusual amino acids.[6] This method makes use of an auxiliary consisting of a bislactimether such as **2**, which can be deprotonated using organolithium reagents (Scheme 2). When the

resulting carbanion is allowed to react with 3-bromoindoles such as **1**, alkylated bislactimethers such as **3** can be obtained. Substituted Trps can then be accessed after cleavage of the auxiliary. For example, Cook and coworkers utilized this method to construct 6-methoxyTrp **4**, which was then used for the synthesis of the natural product tryptostatin A.[7]

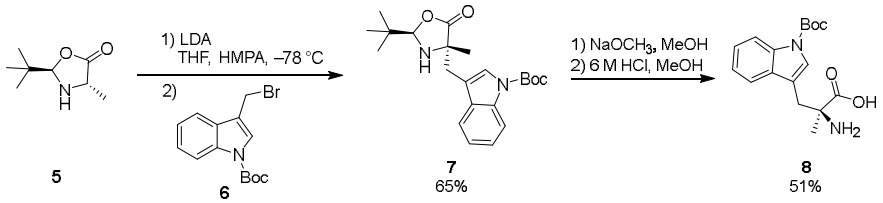


Scheme 1. Overview of the methods discussed in this chapter.



Scheme 2. Synthesis of 6-methoxyTrp by the Schöllkopf method.

For the synthesis of α-methylated Trp **8**, Seebach and coworkers used alanine-derived oxazolidinone **5**, which could be deprotonated using lithium diisopropylamide (LDA) and upon reaction with **6** gave rise to **7**, which was transformed into the *S*-enantiomer of α-methylTrp in 33% yield over three steps (Scheme 3).[8]

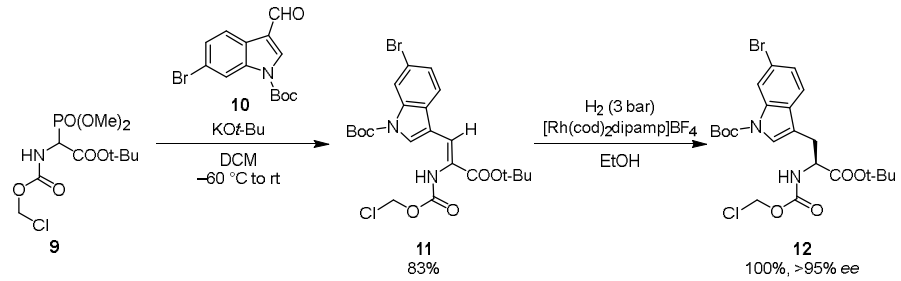


Scheme 3. Synthesis of α-methylTrp.

The disadvantage of auxiliary-based methods lies in the multi-step procedures needed for the construction and cleavage of the auxiliary, which renders these methods rather inefficient compared to other, more recent approaches.

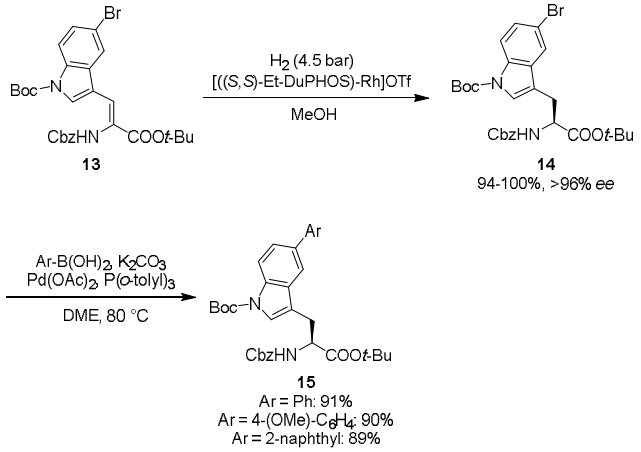
2.2. Enantioselective hydrogenation of dehydroamino acids

α,β-Didehydroamino acids are easily accessible by Horner-Wadsworth-Emmons reaction of glycine-derived phosphonates with aldehydes.[9] When the resulting double bond is hydrogenated in the presence of chiral ligands, the corresponding amino acids can be obtained with high stereoselectivity.[10] For the synthesis of 6-bromoTrp **12**, Schmidt and Wild allowed to react aldehyde **10** with phosphonate **9** in an olefination reaction followed by hydrogenation of the resulting olefin **11** using a nonracemic rhodium catalyst (Scheme 4).[11] The resulting brominated Trp **12** was then used to construct the natural product hexaacetylcelenamide A.



Scheme 4. Synthesis of 6-bromoTrp by enantioselective hydrogenation; cod: 1,5-cyclooctadiene; dipamp: (ethane-1,2-diyl)bis[(2-methoxyphenyl)(phenyl)phosphane].

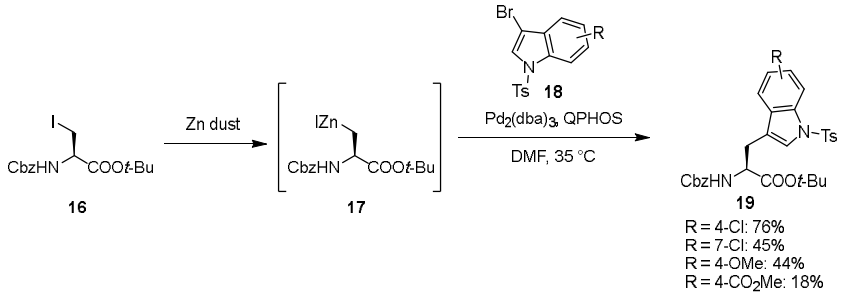
In 2002, Hruby and coworkers demonstrated the synthesis of 5-bromoTrp using a different catalyst system. For the hydrogenation of **13**, they used [((*S*,*S*)-Et-DuPHOS)-Rh]OTf and could obtain the *S*-enantiomer of 5-bromoTrp **14** in high yield and enantioselectivity (Scheme 5).[12] This brominated Trp could then be coupled with different arylboronic acids, giving access to 5-arylTrps **15**. Furthermore, they demonstrated that the enantiomer of the catalyst can be used to prepare the *R*-configuredTrps with the same efficiency.



Scheme 5. Synthesis of 5-arylated Trps by enantioselective hydrogenation followed by Suzuki-Miyaura coupling; [((*S*,*S*)-Et-DuPHOS)-Rh]OTf: 1,2-bis-((2*S*,5*S*)-2,5-diethylphospholano)-benzene-(1,5-cyclooctadiene)-rhodium(I) trifluoromethanesulfonate.

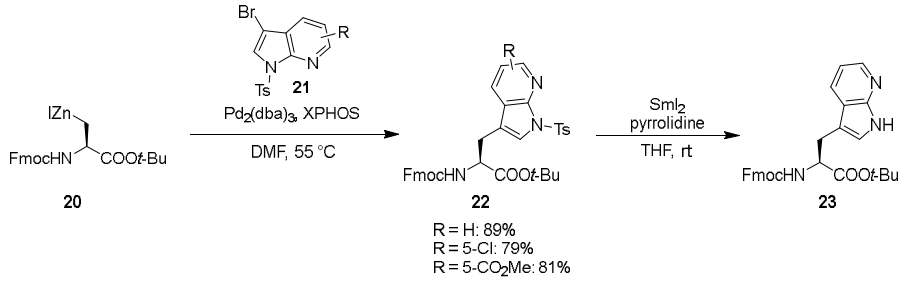
2.3. Negishi coupling

When reacted with activated zinc dust, β-iodoalanine **16**, which itself can easily be prepared from protected serine, gives access to β-zincated alanine derivatives such as **17** (Scheme 6).[13] This metalated amino acid is a versatile building block in transition metal-catalyzed couplings and can for example be used to construct phenylalanine or propargylglycine derivatives.[14] When **17** is reacted with *N*-tosyl protected 3-bromoindole **18** under Pd-catalysis, the Trp derivatives **19** can be obtained in good yields.[15] The same approach has also been used by Payne and coworkers in the synthesis of the natural product Ecumicin, which contains a 4-methoxyTrp building block.[16]



Scheme 6. Synthesis of Trp derivatives by Negishi coupling; Ts: *p*-toluenesulfonyl; dba: dibenzylideneacetone; QPHOS: 1,2,3,4,5-pentaphenyl-1′-(di-*tert*-butylphosphino)ferrocene.

Recently, Roy *et al.* reported the synthesis of different azaTrps **23** using a strategy based on Negishi couplings of azaindoles **21** to β-zincated alanine **20** (Scheme 7).[17] They also demonstrated the orthogonal cleavage of the different protecting groups in **22**, including the Ts group which could be cleaved reductively with SmI_2.



Scheme 7. Synthesis of 7-azaTrps by Negishi coupling; XPHOS: 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl.

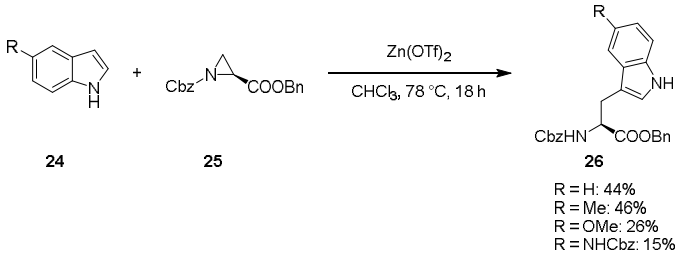
2.4. Aziridine opening

The nucleophilic addition of indoles **24** to serine-derived aziridine-2-carboxylates **25** presents another possibility for the synthesis of Trp derivatives (Scheme 8). The first example using this approach was described by Sato and Kozlowski in 1989.[18] They used an excess of $Zn(OTf)_2$ as a Lewis acid, which afforded the Trp derivatives **26** in moderate yields.

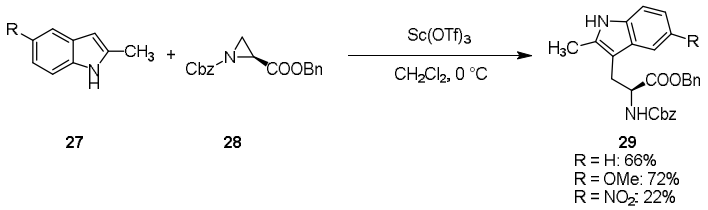
Bennani *et al.* optimized this method using stoichiometric amounts of $Sc(OTf)_3$ instead of Zn-based Lewis acids (Scheme 9).[19] Different indoles **27** were reacted with Cbz- or Fmoc-protected aziridines **28** in the presence of $Sc(OTf)_3$ and delivered the Trps **29** in good yields. When nitro or hydroxyderivatives were used, the yield however dropped significantly, or no product could be isolated.

In 2002, Isobe *et al*. noted that when the methyl aziridine-2-carboxylate was used instead of the benzyl ester **28**, the regioselectivity of the attack (2- *vs.* 3-position on the aziridine) decreased significantly.[20]

By using $Sc(ClO_4)_3$, they could raise this selectivity back to >90:10 and later used this method for the synthesis of *C*-mannosyl-derivatives of Trp.[21,22]

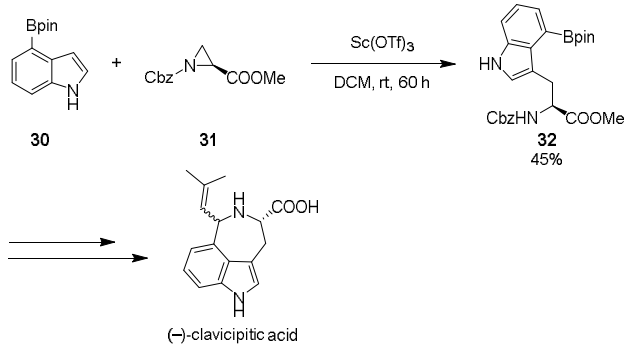


Scheme 8. $Zn(OTf)_2$-Promoted nucleophilic aziridine opening.



Scheme 9. $Sc(OTf)_3$-Promoted aziridine opening.

For the synthesis of (–)-clavicipitic acid, Piersanti *et al*. made use of the Sc(III)-promoted aziridine opening. They reacted 4-borylated indole **30** and aziridine **31** in the presence of $Sc(OTf)_3$ to synthesize 4-borylated Trp derivative **32**. This compound was then transformed into the natural product in only four additional steps (Scheme 10).[23]



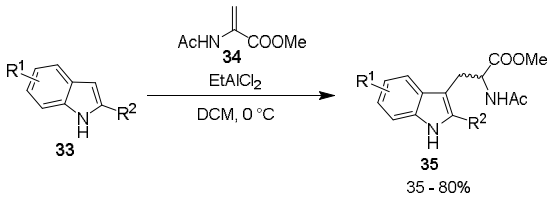
Scheme10. Synthesis of (–)-clavicipitic acid *via* aziridine opening.

2.5. Friedel-Crafts conjugate addition to 2-aminoacrylates

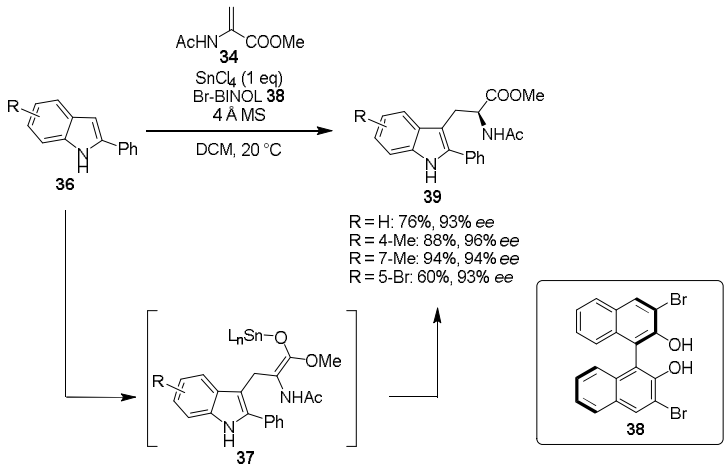
Another approach using indoles **33** as electrophiles is based on a Friedel-Crafts conjugate addition to 2-aminoacrylate derivatives such as **34** (Scheme 11). This approach was pioneered by Piersanti *et al.* in 2008,[24] who utilized Lewis acids such as $EtAlCl_2$ to form the desired addition products **35** in good yields. The Trps were however only obtained in their racemic forms. The same authors later used this method to prepare borylated DL-Trps suitable for Suzuki-Miyaura couplings.[25]

An enantioselective variation of this method was first described by Reisman and coworkers in 2012.[26] To obtain one enantiomer of Trps selectively, the protonation of tin enolate **37** (resulting from the addition of indole **36** to aminoacrylate **34**) has to be performed asymmetrically (Scheme 12). This could be

accomplished by employing (*R*)-3,3'-dibromo-BINOL **38** as a ligand for the tin-enolate, which forces protonation from the *Si*-face. The resulting Trp derivatives **39** could thus be obtained in very good yields and enantiomeric excesses.



Scheme 11. Trp-Synthesis by Friedel-Crafts conjugate addition.



Scheme 12. Trp-Synthesis by asymmetric Friedel-Crafts conjugate addition.

2.6. β-C(sp^3)–H activation of alanine derivatives

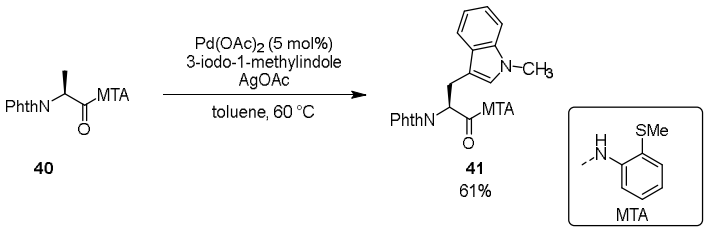
The introduction of indole into the side chain of amino acids or peptides can also be accomplished by C–H activation of an alanine derivative in the β-position, followed by cross-coupling with 3-iodoindole. In this case, a directing group at the C-terminal end of the amino acid is necessary to obtain selectivity in the C–H activation step. Amides of 8-aminoquinoline (AQ) or 2-(methylthio)-aniline (MTA) are typically used for this purpose. MTA amides usually yield a higher selectivity towards mono-substitution of the alanine CH_3-group.[27]

The first example of a Trp derivative prepared by β-C–H-activation was reported by Tran and Daugulis in 2012.[27] They used MTA as a directing group on phthaloyl protected alanine **40**, which was then reacted with 3-iodo-1-methylindole yielding 1-methyTrp **41** in a good yield (Scheme 13). Two years later, Chen *et al*. reported a similar approach using AQ as a directing group and *N*-tosyl-3-iodoindole as the coupling partner.[28]

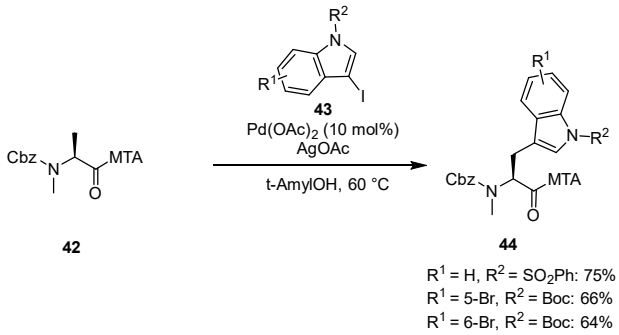
Kinsinger and Kazmaier later extended this methodology to *N*-methylated alanine MTA amides such as **42** in the C–H activation reaction (Scheme 14).[29] They also observed a high selectivity for the mono- *vs.* double C–H activation. Furthermore, brominated 3-iodoindoles **43** could be coupled to alanine, giving access to brominated Trps **44** in good yields.

During synthetic studies towards the natural product inducamide C, Sperry *et al*. used a C–H activation approach to prepare substituted Trp derivative **47** (Scheme 15). The reaction of alanine derivative **45** with 3-iodoindole **46** in the presence of $Pd(OAc)_2$ and AgTFA delivered **47** in a good yield. With this compound,

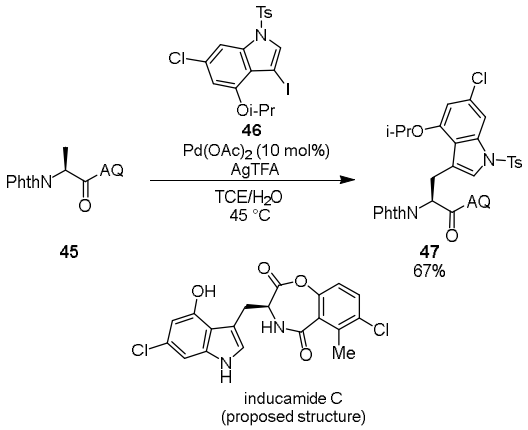
they attempted the synthesis of inducamide C, but did not succeed in accessing the natural product, possibly due to erroneous structure elucidation or low stability of the compound.[30]



Scheme 13. Synthesis of 1-methylTrp by β-C–H-activation.



Scheme 14. Synthesis of *N*-methylated Trp derivatives by β-C–H-activation.

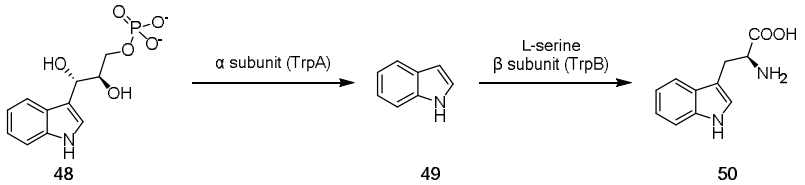


Scheme 15. Synthesis of substituted Trp **47** for studies towards the synthesis of inducamide C.

2.7. Enzymatic approaches

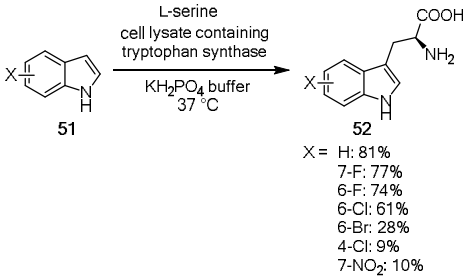
Biosynthetically, Trp is produced by the enzyme tryptophan synthase (TrpS). TrpS is a heterodimer consisting of two subunits, which catalyze different reactions. While the α-subunit (TrpA) catalyzes the transformation of indole-3-glycerol phosphate **48** to indole **49**, the β-subunit (TrpB) is responsible for the reaction between the resulting indole and L-serine, forming Trp **50** as a product (Scheme 16). In this reaction, an aminoacrylate intermediate is formed by elimination of H_2O from serine, which then reacts in a Friedel-Crafts conjugate addition with indole.[31]

This biocatalytic reaction sequence has been used to prepare numerous derivatives of Trp, the first examples being reported as early as the 1960s and 1970s.[32,33] In these reports, mostly 5- and 6-substituted indoles were used.



Scheme 16. Reactions catalyzed by the subunits of TrpS.

In 2006, Goss and Newill reported on the use of cell lysate containing TrpS as a practical alternative to the use of purified enzymes.[34,35] They allowed to react different halo- and methylindoles **51** with serine to form the corresponding Trp derivatives **52**. The yields were usually highest when 5- or 6-substituted indoles were used compared to 7- or 4-substituted indoles. This was attributed to the increased size of the indole, hindering the passage through a tunnel from TrpA to the TrpB subunit. Later, they described that a change of the host organism (a different strain of *E. coli*) not only increased the yields of the Trp derivatives, but also enabled the synthesis of 7-haloTrps (Scheme 17).[36] The yields for electron-deficient (NO_2-substituted) indoles or those bearing large substituents could however not be improved much.



Scheme 17. Biocatalytic synthesis of Trp derivatives using TrpS.

Arnold and coworkers set off to improve the substrate promiscuity of TrpS by directed evolution. They first attempted to make the β-subunit independent of the α-subunit through mutation. When not in complex with each other, the two subunits have only low catalytic activities, which increase dramatically as soon as both subunits are present. By mutating the enzyme in three rounds of directed evolution, Arnold *et al*. were able to increase the activity of a stand-alone TrpB (the new version was termed *Pf*TrpB^{0B2}) to the level of the heterodimeric TrpS complex. They found that the new mutations were mimicking the binding of TrpA to TrpB and thus activating the enzyme similar to an allosteric interaction.[37]

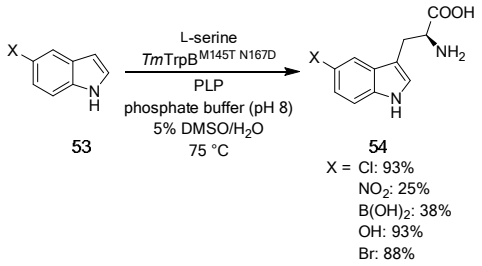
The beneficial mutations were later also incorporated into homologues of TrpB from different organisms. A mutated variant from *Thermotoga maritima* (*Tm*TrpB$^{M145T\ N167D}$) was especially useful for the synthesis of 5-substituted Trps **54** from different indoles **53**, showing an even higher activity for challenging 5-bromoindole compared to naked indole (Scheme 18).[38]

Further directed evolution of TrpB led to new biocatalysts, which enable the synthesis of a broad range of β-branched or heteroatom-containing Trps and related amino acids. These biocatalysts can also be used in enzyme cascades, providing access to *e.g.* D-amino acids or tryptamines.[39]

3. Indole synthesis in the side chain of amino acids or peptides

In contrast to the approaches based on C–C bond formation, the synthesis of the indole ring system on the amino acid or peptide backbone allows for the late-stage modification of peptides or natural products. Despite a large number of previously described indole syntheses, only a few of these can however

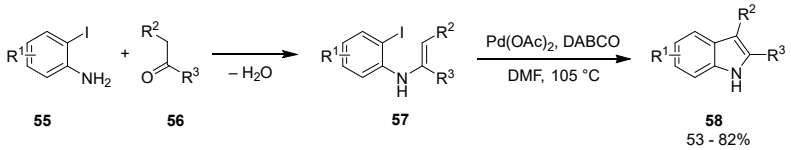
selectively produce 3-substituted indoles, which is required for the synthesis of Trp derivatives.[40] The first approaches to access Trps by indole synthesis used the classical Fischer conditions, in which aryl hydrazines are reacted with enolizable ketones.[41,42] This reaction however asks for quite harsh conditions (*i.e.* the addition of Lewis or Brønsted acids). Therefore, these protocols are generally less suitable for highly elaborate substrates, such as precursors of natural products.



Scheme 18. Biocatalytic synthesis of 5-substituted Trps; PLP: pyridoxal phosphate.

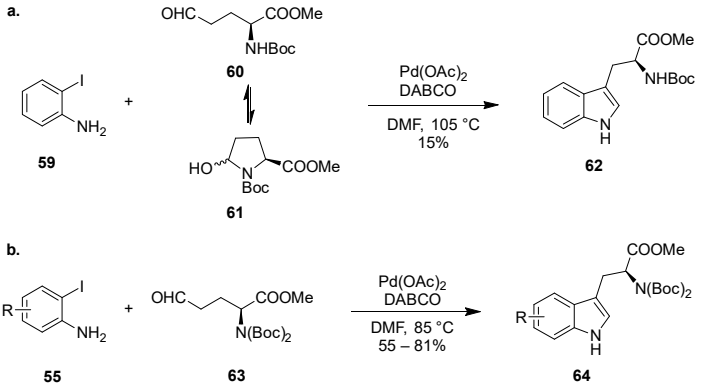
3.1. Starting from δ-oxoamino acids

In 1998, Chen *et al.* described a Pd-catalyzed synthesis of indoles starting from *o*-iodoanilines **55** and carbonyl compounds **56** (Scheme 19).[43] In this reaction, the formation of the indole **58** results from an intramolecular Heck-coupling of enamine **57** which is formed *in situ*.



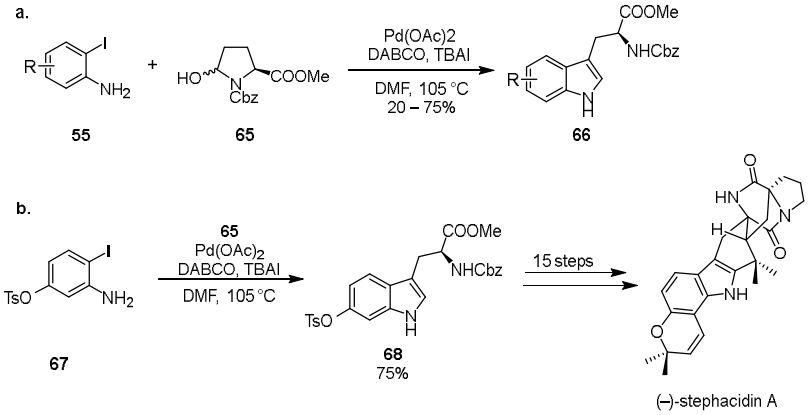
Scheme 19. Pd-Catalyzed indole synthesis from iodoanilines and ketones.

Zhu and Jia applied these reaction conditions to the synthesis of Trps using 2-iodoaniline **59** and Glu-derived aldehyde **60** (Scheme 20).[44] The yield of Trp **62** was however rather low in this reaction. They attributed this to the equilibrium between aldehyde **60** and semi-aminal **61** that may hinder the formation of the required enamine. They tried to prevent this by using double Boc-protected aldehyde **63**, which delivered the Trps **64** in good yields at a reaction temperature of 85 °C. Based on this work, Campagne *et al.* described the synthesis of a central building block of the natural product celogentin C.[45]



Scheme 20. Pd-Catalyzed Trp-synthesis by Zhu and Jia.

Baran *et al*. also reported on the synthesis of Trp derivatives based on Chen's indole synthesis. Similar to Zhu and Jia, they could only isolate the Trp derivatives in low yields when hemiaminal **65** was reacted with iodoanilines **55** under Chen's reaction conditions (Scheme 21a). A thorough analysis of the byproducts formed during the reaction revealed that a deiodination of the enamine intermediate took place. By adding tetrabutylammonium iodide (TBAI) to the reaction mixture, this side reaction could be suppressed, resulting in good yields of the desired Trps **66**. Based on Zhu's and Jia's results with double protected amino acid **65**, it seems likely that the proto-deiodination is facilitated by the N-H of the amino acid (or the O-H of the semi-aminal). Baran and coworkers also utilized this method for the construction of (–)-stephacidin A from 5-tosyloxyTrp **68**, which was prepared from iodoarene **67** and hemiaminal **65** (Scheme 21b).



Scheme 21. a. Trp-Synthesis using TBAI as an additive (R=OTs, F, OMe, Me, Cl); b. Synthesis of (-)-stephacidin A.

A remarkable application of this Trp synthesis was described by Suh *et al.* in their total syntheses of ohmyungsyamycins A and B (Scheme 22).[46] These cyclic depsipeptides contain an unusual 4-methoxyTrp unit, which was constructed by Suh and coworkers in the side chain of aldehyde-bearing tetrapeptide **70**, obtained by Lemieux oxidation of an olefinic precursor. Then, **70** was reacted with 2-iodo-3-methoxyaniline **69** under Chen's reaction conditions to yield Trp derivative **71** in 59% yield. Eight further steps led to the natural products ohmyungsamycin A and ohmyungsamycin B, whose structures were revised.

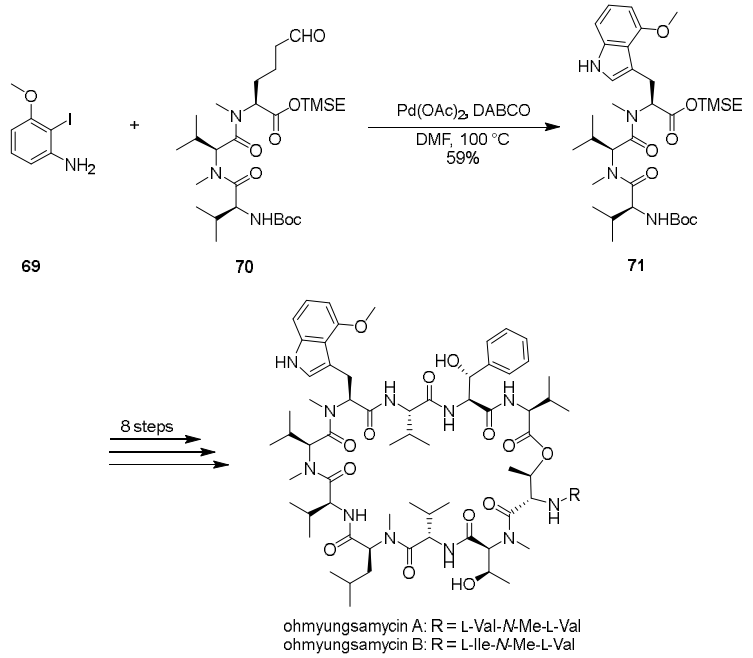
3.2. Larock indole synthesis

Larock's indole synthesis utilizes *o*-halogenated anilines in combination with internal alkynes, which form 2,3-disubstituted indoles under Pd-catalysis. When silyl-substituted alkynes are used, the obtained indoles carry the silyl substituent in 2-position, whereas the other residue is placed in 3-position.[47,48] This can be used for the synthesis of Trps, as has been demonstrated by Gronowitz *et al*. in 1993.[49] They used racemic, silylated propargylglycine **72** and substituted iodoanilines **55** to form the 2-silylatedTrps **73**, which can be transformed to Trp-derivatives **74** using $AlCl_3$ (Scheme 23). The overall yields of this sequence were however rather low.

Cook and coworkers demonstrated the use of Larock's indole synthesis for the preparation of enantiomerically enriched Trps by using Schöllkopf-auxiliary derived alkyne **75** together with different iodoanilines **55** (Scheme 24).[50] They found that a TES-protecting group on the alkyne resulted in the best regioselectivities for 2-silylated indole **76** in the annulation reaction. The silyl group and the chiral auxiliary could be cleaved with TBAF and aqueous HCl solution, yielding the Trps **77** in good yields. Boder *et al*. used a similar strategy in their syntheses of the natural products chloropeptine I and II.[51]

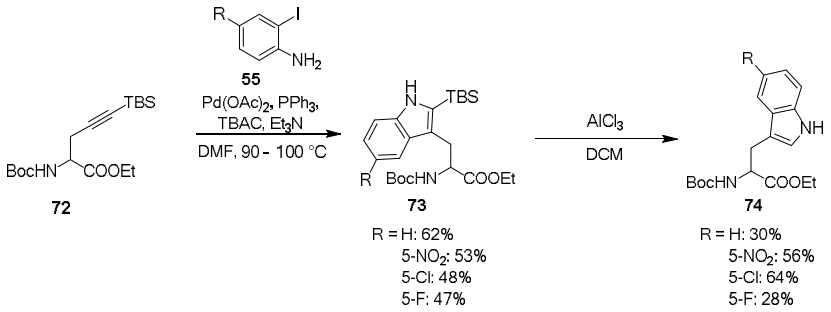
Larock's indole synthesis has also been applied on short peptides. In the total synthesis of kapakahines B and F, Baran *et al.* used a Larock indole synthesis to construct the bridging Trp moiety in the natural

products.[52] Tripeptide **78** was reacted with **79** under addition of $Pd(OAc)_2$, LiCl and NaOAc (Scheme 25). However, 2.2 equivalents of **78** had to be used to obtain a yield of 49% of the product. The natural products kapakahines B and F were then obtained in two and three steps from **80**, respectively.



69 **70** **71**

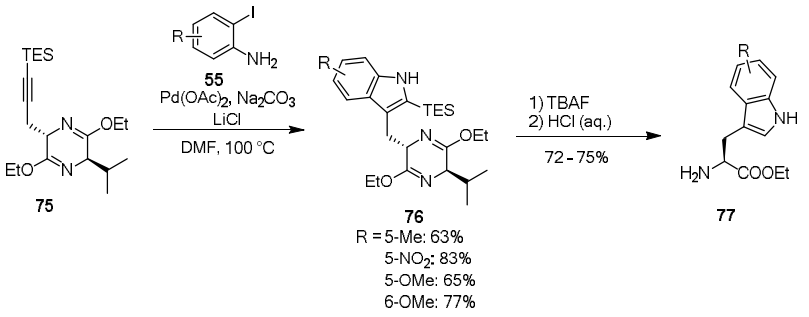
Scheme 22. Total synthesis of ohmyungsamycins A and B.



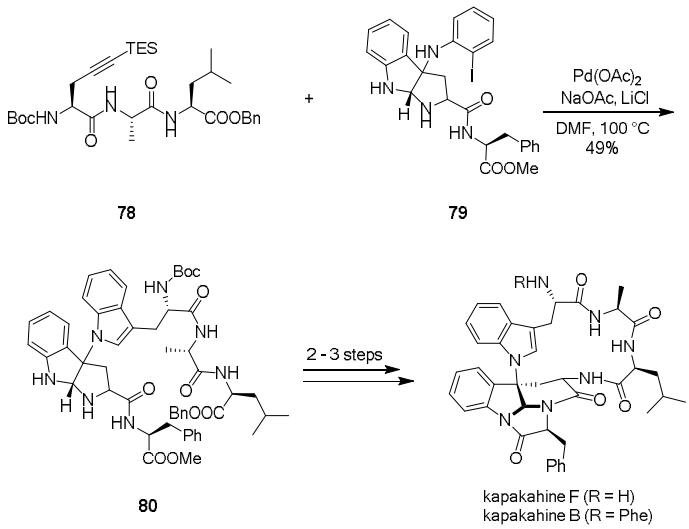
72 **73** **74**

Scheme 23. Racemic Trp-synthesis based on Larock's indole synthesis; TBAC: tetrabutylammonium chloride.

In 2016, Reisman and coworkers presented a mild and general protocol for the synthesis of Trps **83** from bromoanilines **81** and TES-propargylglycines **82** (Scheme 26a).[53] By using the electron-rich ligand $P(t\text{-}Bu)_3$, or the corresponding palladium complex $Pd[P(t\text{-}Bu)_3]_2$, the less reactive bromoanilines reacted at only 60 °C. This method proved to be effective for the synthesis of a broad range of Trps bearing substituents in every possible position. Even azaTrps and benzofuranes could be accessed this way. Reisman *et al.* further showcased the usefulness of this method by synthesizing natural product (-)-aspergilazine A in a concise synthesis from bromoaniline **84** and diketopiperazine **85** (Scheme 26b).



Scheme 24. Trp-Synthesis based on Schöllkopf auxiliary and Larock's indole synthesis.



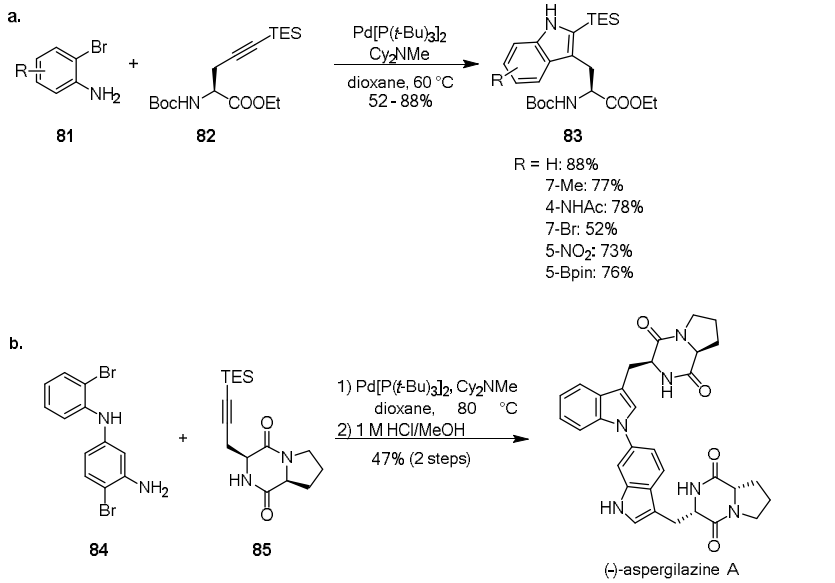
Scheme 25. Synthesis of kapakahines B and F based on Larock's indole synthesis.

The naturally occurring cyclic peptide streptide contains an uncommon lysine-Trp linkage in its core. Boger and coworkers synthesized the natural product using a modified version of Reisman's protocol.[54] For the cyclization of **86** to macrocycle **87**, they had to use stoichiometric amounts of Pd(P*t*-Bu$_3$)$_2$ under high dilution conditions to obtain a yield of 60% (Scheme 27). After this annulation step, only four further steps led to the proposed structure of the natural product, which turned out not to be identical to the natural material. The structure of streptide could then be revised by synthesis of an epimer with the opposite configuration in the β-position of the lysine unit.

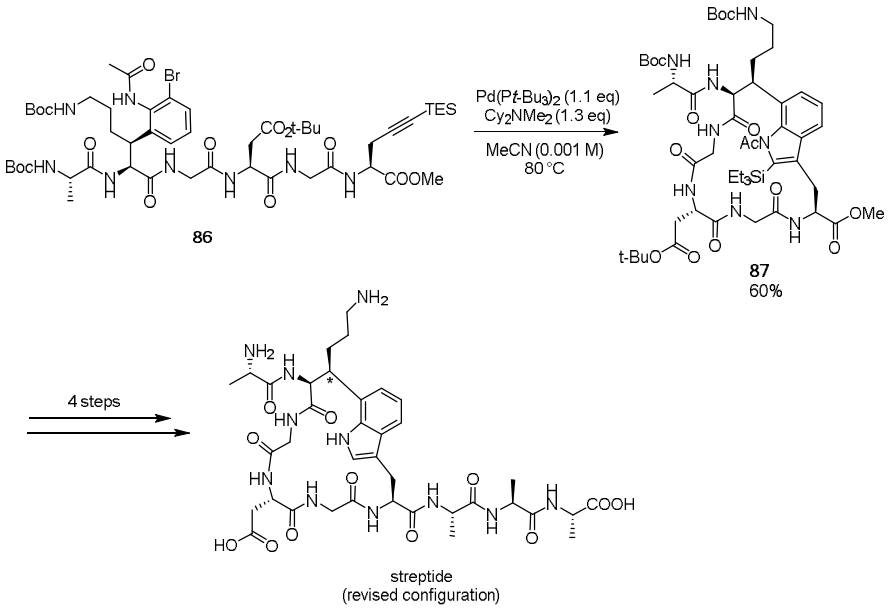
3.3. Based on stannylated allylglycines

Stannylated allylglycines as versatile building blocks can be obtained by Pd-catalyzed allylic alkylation (Tsuji-Trost reaction) of chelated glycine enolates such as **89**, which can be obtained by deprotonation of glycine **88** in the presence of $ZnCl_2$. Upon reaction with stannylated allylic substrate **90**, the metalated amino acid **91** can be obtained in good yields (Scheme 28a).[55,56]

When dipeptide enolates are used in this reaction, the corresponding (*S,R*)-stannylated peptide **94** is formed in high yields and diastereoselectivities since one side of the enolate is shielded by the side chain of the other amino acid in the peptide (Scheme 28b).[57] The organotin compounds **89** and **94** are suitable for various cross-coupling reactions under mild conditions, providing access to a divserse set of unusual amino acids and peptides.



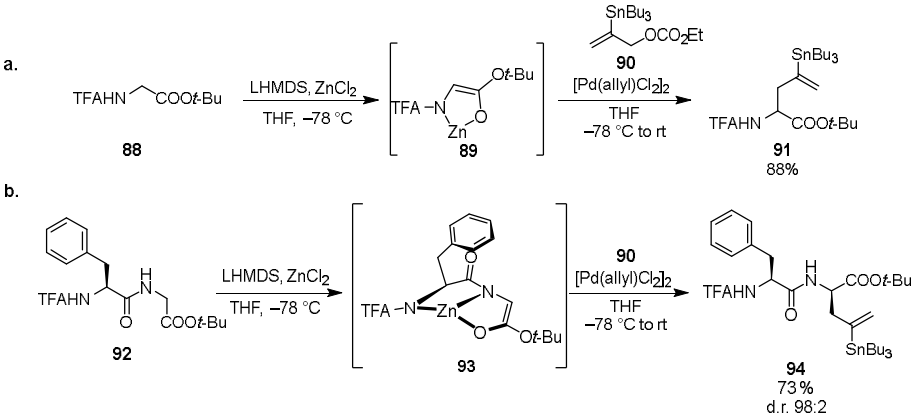
Scheme 26. a. Mild Pd-catalyzed procedure for the synthesis of Trps;
b. Total synthesis of (-)-aspergilazine A.



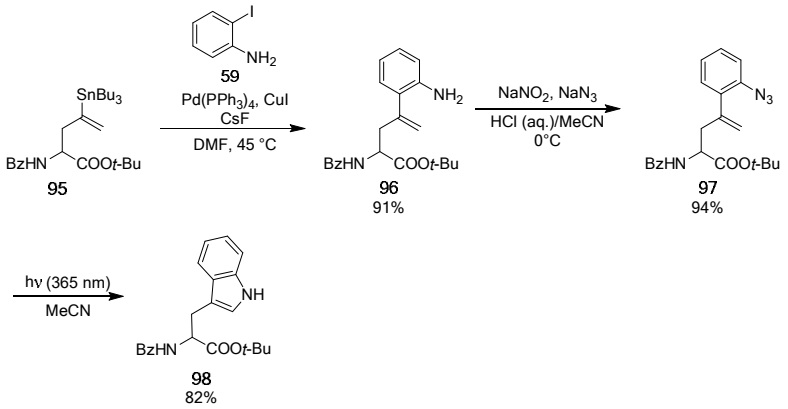
Scheme 27. Total synthesis and configurational revision of streptide based on Larock's indole synthesis.

Junk and Kazmaier made use of these organotin species for the synthesis of substituted Trp derivatives.[58] They coupled stannylated allylglycine **95** with *o*-iodoaniline **59** and subsequently exchanged the NH_2 in **96** group to an azido group by diazotation and azidation (Scheme 29). Interestingly, the azido compound **97** spontaneously formed traces of the desired Trp derivative **98** under ambient light. Since this

reaction most likely proceeds *via* a light-induced nitrene C–H insertion, a UV-LED (λ=365 nm) was used as a mild light source, providing Trp **98** in a good yield.



Scheme 28. a. Preparation of stannylated allylglycines; b. Stereoselective allylic alkylation of dipeptide enolates.



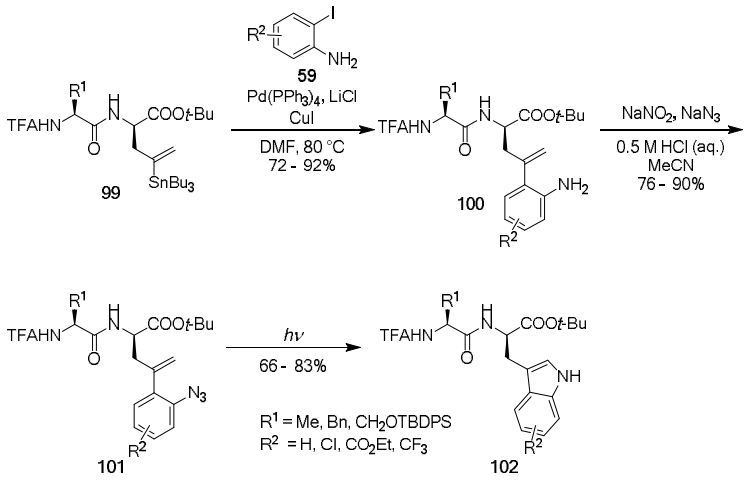
Scheme 29. Synthesis of racemic Trp from stannylated allylglycine.

This protocol was also applied to dipeptides **99** carrying the stannylated allyl side chain and proceeded with the same efficiency (Scheme 30).[59] Here, the Stille coupling with **59** had to be done under base-free conditions (without the addition of CsF) to obtain **100** in good yields. The azidation to **101** and photochemical nitrene insertion to form the Trps in **102** proceeded with good yields. Additionally, different substituents on the *o*-iodoanilines **59** were stable under these reaction conditions. Thus, access to (*S*,*R*)-configured Trp-dipeptides **102** was established.

After having developed this method, the natural products keramamides A and L and mozamide A sparked the interest of Junk and Kazmaier. These compounds belong to the large class of anabaenopeptin-type peptides and contain substituted, *N*-methylated Trp moieties (Figure 1).[60-62]

To synthesize these natural products and derivatives thereof *via* stannylated allylglycines, the allylic alkylation strategy could however not be used since the Trp-units as well as their neighboring amino acids are all *S*-configured in these compounds. For the synthesis of keramamide L, Junk and Kazmaier thus chose a strategy based on propargylglycine containing cyclic peptide **103** (Scheme 31).[63] The conditions of the following reactions had to be carefully chosen to avoid base-induced hydantoin formation of the urea side

chain. A Ru(II)-catalyzed hydrostannation to form organotin compound **104** was followed by a CuTC/$Ph_2PO_2NBu_4$-mediated Stille cross-coupling to obtain aniline **105**. Diazotation/azidation to form azide **106** and subsequent photochemical nitrene insertion gave rise to Trp derivative **107**. Final deprotection of the side chain then delivered keramamide L. The configuration of the natural product could additionally be revised by the synthesis of diastereomers bearing an *R*-configured lysine unit. Keramamide A was synthesized from the same precursor **104** by using a different *o*-iodoaniline.



Scheme 30. Synthesis of modified Trp-containing dipeptides.

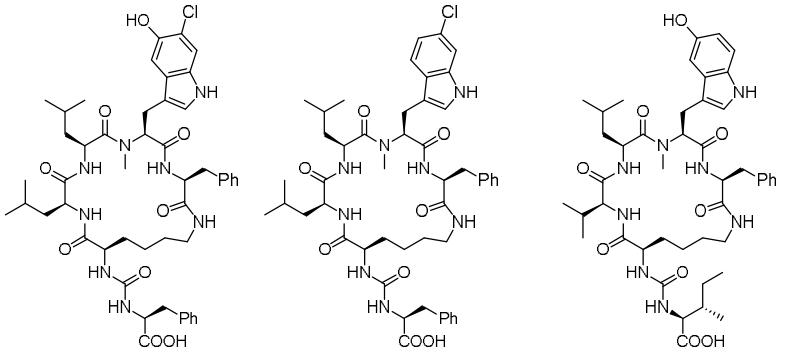


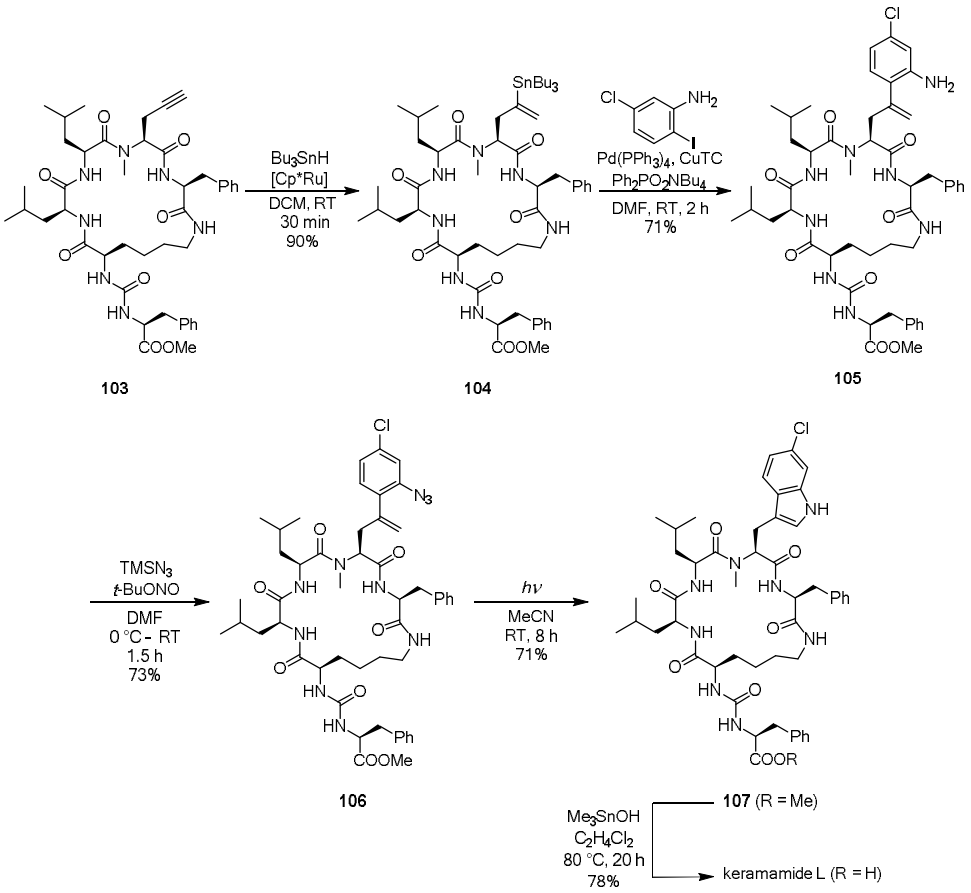
Figure 1. Revised structures of the keramamides A and L as well as mozamide A.

Mozamide A, being structurally similar to the keramamides, could be synthesized using the same strategy. In this case, the configuration of three amino acids could be revised by total synthesis.[64] These examples show that the synthesis of Trp derivatives based on stannylated allylglycines is a robust method enabling the late-stage construction of indoles and therefore the preparation of natural product derivatives.

4. Substitution of Trp by C(sp^2)–H activation

The indole moiety of Trp can be functionalized by transition metal-catalyzed C(sp^2)−H activation. In this case, there is typically no need for an elaborate preactivation of the substrate. This type of functionalization is therefore very suitable for the late-stage modification of Trp in peptides.[65,66] The most

prominent position for C(sp^2)−H activation in Trp is the C2 position in the pyrrole part of the 3-substituted indole ring. Hence, several methods for the formation of C–C bonds in this position were established.

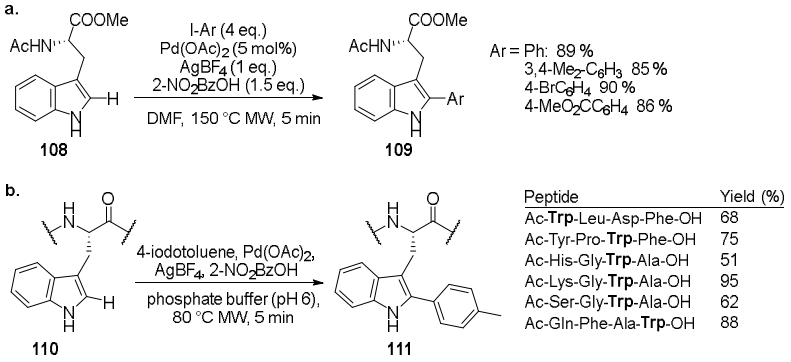


Scheme 31. Synthesis of keramamide L *via* stannylated intermediate; Cp*: pentamethylcyclopentadienyl; CuTC: copper(I) thiophene-2-carboxylate.

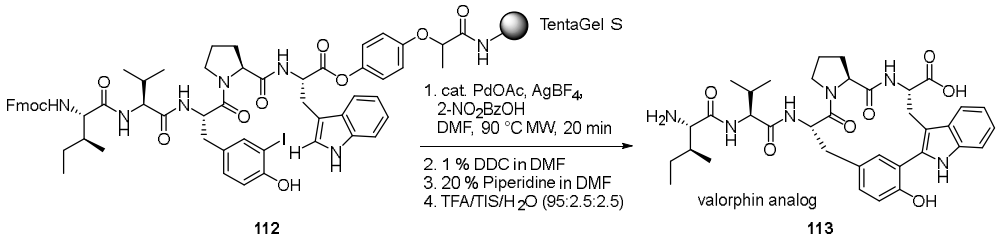
In 2010, Albericio and Lavilla *et al.* prepared different 2-arylated Nα-acetylTrps **109** *via* Pd(II)-catalyzed C−H activation of protected Trps **108** (Scheme 32a).[67] They shortened the reaction time from 24 h to 5 min using microwave (MW) irradiation. This direct arylation could also be applied to Trp-containing peptides **110** in aqueous media to obtain 2-arylated Trp-containing peptides **111** (Scheme 32b). For this reaction, the position of the Trp-unit in the peptide sequence did not play any role. Later, they were able to expand their method to include Nα-TFA or Nα-Fmoc protected and even unprotected Trps.[68]

Conformationally stabilized peptides have the potential to provide improved pharmacokinetic properties such as, *inter alia*, to show better proteolytic stability. Albericio and Lavilla *et al.* applied their method of C2 arylation of Trp to the synthesis of stapled peptides which are constrained by a linkage between two sidechains, in their case between Trp and Phe or Tyr, respectively.[69] They synthesized peptides containing Trp and iodo-phenylalanine (or iodo-tyrosine) and coupled them through intramolecular Pd-catalyzed C−H activation reaction. It could be shown that the process can be used in solution and even in solid-phase synthesis, as shown for the stapled version of a bioactive valorphin analog **113** synthesized from its linear resin bound precursor **112** (Scheme 33).

Similar methods for the Pd-catalyzed C2 arylation of Trps that use other arylating reagents like (un)symmetrical diaryliodonium salts[70-72] and aryldiazonium salts[73] instead of aryl iodides have been developed by the groups of Fairlamb and Ackermann. No additional stochiometric silver salt is required in these processes.

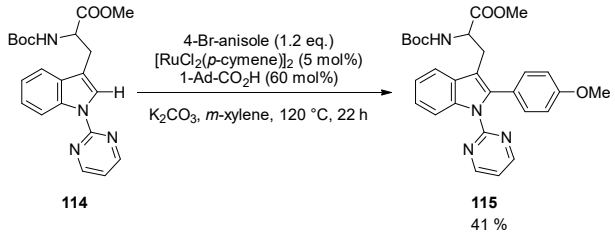


Scheme 32. a. Pd-Catalyzed arylation of AcTrpOMe in C2 position *via* C−H activation; b. Arylation of Trp in peptides by Pd-catalysis in aqueous media.



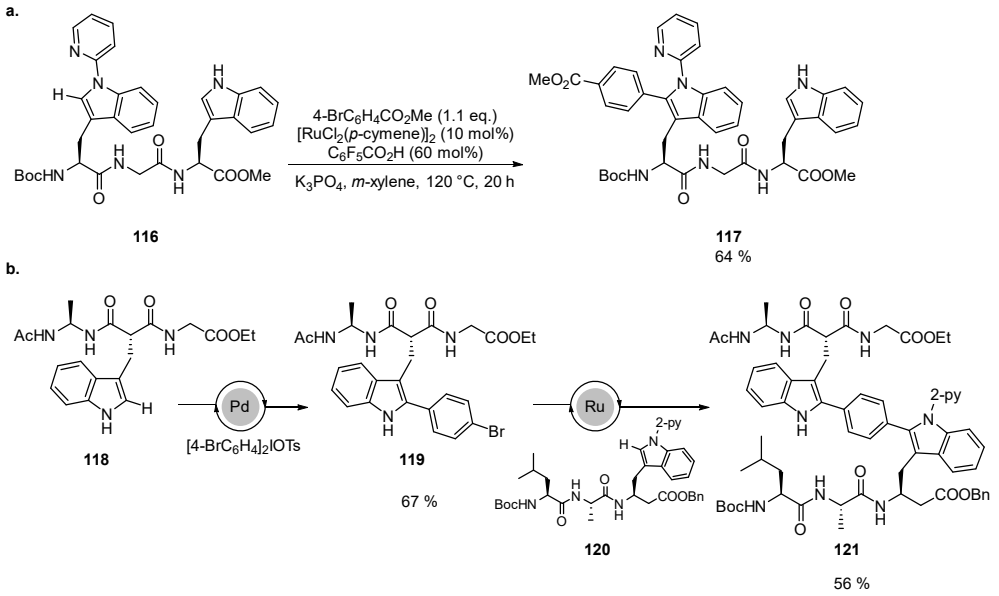
Scheme 33. On-resin synthesis of a valorphin analog as stapled peptide *via* intramolecular Pd-catalyzed arylation between the C2 position of Trp and 3-I-Tyr; DDC: sodium diethyldithiocarbamate; TFA: trifluoroacetic acid; TIS: triisopropylsilane.

Ackermann and Lygin developed a method for Ru(II)-catalyzed C−H activation of indoles.[74] They used 2-pyridyl or 2-pyrimidyl residues at N1 as removable directing groups in the arylation of the C2 position. This method could be applied to the arylation of Trp derivative **114** to arylated Trp **115** (Scheme 34).



Scheme 34. Ru-Catalyzed arylation of BocTrpOMe in C2 position *via* 2-pyrimidyl-directed C–H activation; Ad: adamantyl.

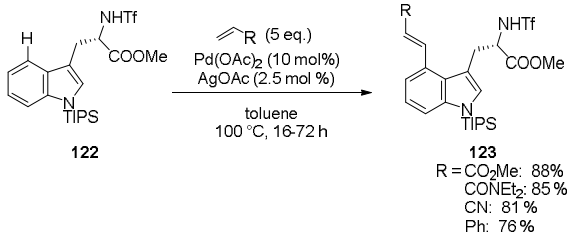
The directing group on the indole nitrogen allowed for the differentiation of Trp in a peptide with more than one Trp-unit. This was demonstrated with the Ru-catalyzed C−H activation of *N1*-2-pyridylTrp next to unsubstituted Trp in **116**, yielding mono-arylated peptide **117** (Scheme 35a).[75] Also, a multi-catalytic C−H activation sequence was investigated to bioorthogonally ligate two different peptides. Tripeptide **118** was first arylated under Pd catalysis to form **119**, which was then reacted with **120** to **121** under Ru catalysis, showcasing the complementarity of Pd and Ru catalysts in these reactions (Scheme 35b).



Scheme 35. a. Chemoselective Ru-catalyzed arylation *via* 2-pyridyl-directed C-H activation; b. Sequential Pd- and Ru-catalyzed arylations for peptide ligation; Ts: *p*-toluolsulfonyl; 2-py: 2-pyridyl.

In addition to Pd and Ru, other metals like Mn,[76–79] Au,[80,81] Co,[79] Rh,[82] and Cu[83] can also be used to functionalize Trp in the C2 position by transition metal-catalyzed C–H activation. For example, alkynylations,[78,80,81] olefinations,[84] alkylations,[85] allylations,[77,79,86] trifluoromethylation[83] and cyanation[76] have been explored.

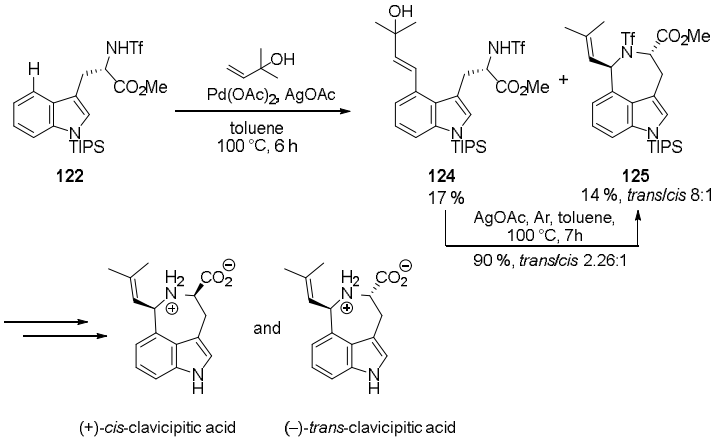
It is more difficult to functionalize the benzoid positions of Trp (C4-C7) with transition metal catalysis than the pyrrole C2 position. Nevertheless, some methods have been elaborated to reach these positions. For the olefination of the C4 position, Jia *et al.* established a Pd-catalyzed directing-group assisted C−H activation (Scheme 36).[87]



Scheme 36. Pd-Catalyzed olefination in C4 position *via* C–H activation; Tf: trifluoromethanesulfonyl; TIPS: triisopropylsilyl.

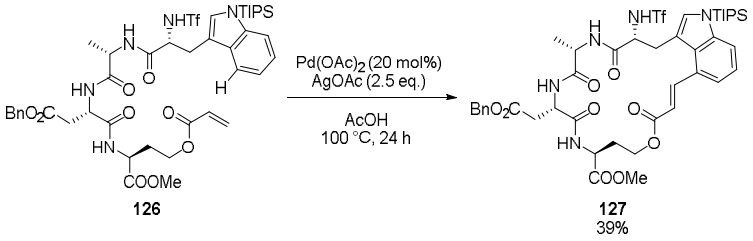
A trifluoromethanesulfonylamide (TfNH) residue at the α-amino functionality in **122** displays a suitable directing group, making it possible to obtain 4-substituted Trps **123** in one step. Furthermore, the shielding of the C2 position with a bulky protecting group such as TIPS at the indole nitrogen is important to achieve a good regioselectivity.

Jia and coworkers aimed to apply their methodology of direct C4 olefination of Trp to the biomimetic synthesis of clavicipitic acid, an indole alkaloid derived from Trp with a hemiterpene moiety.[87] The olefination of **122** with 2-methyl-3-buten-2-ol resulted in allylic alcohol **124**, which could be transformed into the cyclized product **125**, which also arose in the C4 functionalization step (Scheme 37). After two further steps, the diastereomers could be separated and independently transformed into (+)-*cis*-clavicipitic acid and (−)-*trans*-clavicipitic acid.



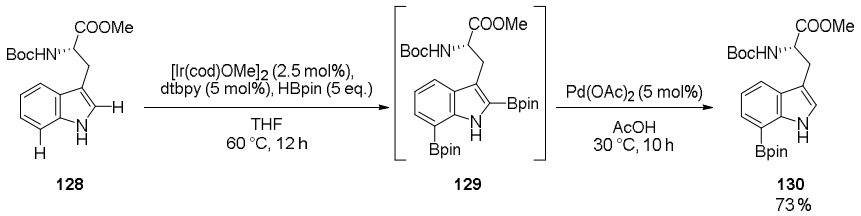
Scheme 37. Synthesis of clavicipitic acid based on a Pd-catalyzed direct Trp-olefination in C4 position *via* C–H activation.

In 2020, Wang and coworkers extended this C4 selective direct olefination to a late-stage macrocyclization of peptides.[88] They cyclized tri- or tetrapeptides such as **126**, which were constructed with Tf-Trp(TIPS) at the *N*-terminus and a sidechain acrylated amino acid (serin, homoserine or lysin) at the *C*-terminus (Scheme 38). This cyclization gave rise to cyclic peptide **127** in a yield of 39%. Recently, Ge and Chen *et al.* found out that also 4-nitrobenzenesulfonyl (Ns) amides can act as a directing group, with the advantage that the Ns-group can easily be removed.[89]



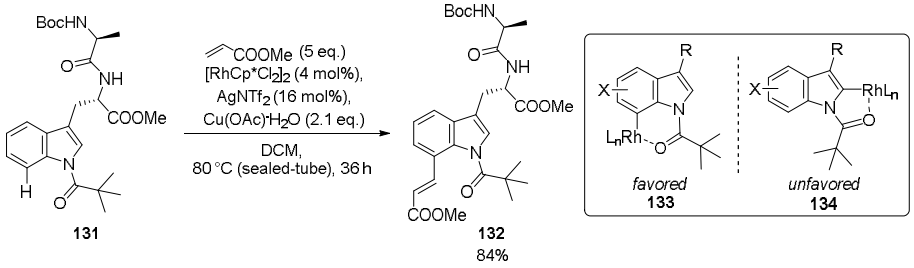
Scheme 38. Macrocyclization *via* late-stage intramolecular Pd-catalyzed olefination of Trp in C4 position.

An approach to functionalize Trp in C7 position was described by Movassaghi and coworkers in 2014.[90] They established a two-step, one-pot procedure to generate C7-borylated Trp **130** which can easily be derivatized (Scheme 39). It was possible to diborylate Boc-Trp-OMe **128** in positions C2 and C7 to **129**. Optimal conditions for protodeborylation of **129** at C2 in presence of the Boc-protecting group were found with catalytic amounts of $Pd(OAc)_2$ in AcOH.



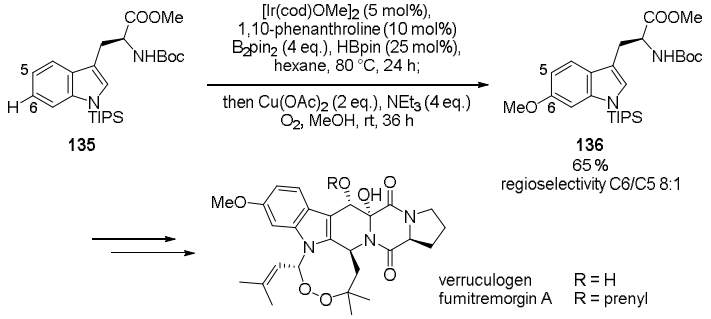
Scheme 39. Synthesis of C7-borylated Trp *via* a two-step, one-pot procedure; cod: 1,5-cyclooctadiene;dtbpy: 4,4'-di-*tert.*-butyl-2,2'-bipyridine; pin: pinacol.

During their studies, Ma *et al.* found out that Rh-catalysis delivers direct C7 olefination of indoles with high regioselectivity when *N*-pivaloyl is used as a directing group.[91] This method of C–H activation is applicable to Trp, as an amino acid or in a peptide, such as Boc-Ala-Trp(Piv)-OMe **131** (Scheme 40). The regioselectivity for the C7 functionalization, delivering **132**, was explained by six-membered intermediate **133**, which could be favored over five-membered intermediate **134** because of the bulky *tert*-butyl group and a suitable catalyst.



Scheme 40. Rh-Catalyzed C7 olefination of *N1*-pivaloyl Trp.

So far, only the group of Baran demonstrated the synthesis of a 6-substituted Trp through C−H activation.[92] With the aim to synthesize the alkaloids verruculogen and femitremorgin A, they explored a method to get access to 6-methoxyTrp **136**. The C2 and C7 positions in Trp were blocked with TIPS as a bulky protecting group at the indole nitrogen **135**, and the reaction conditions for an Ir-catalyzed borylation were optimized by ligand tuning with regard to the regioselectivity between C5 and C6 (Scheme 41). The best regioselectivity ratio in favor of the C6-borylated Trp they obtained was 8:1. Immediately afterward, a Chan-Lam coupling with methanol was carried out to provide the 6-methoxyTrp **136**, from which Baran and coworkers could synthesize the natural products in seven or eight additional steps, respectively.



Scheme 41. Synthesis of verruculogen and fumitremorgin A based on an Ir-catalyzed C6-selective borylation of *N1*-TIPS-protected Trp, followed by Chan-Lam-coupling.

5. Conclusion

To synthetically access the diversity of substituted Trps and indole derivatives in natural products, numerous different methods have been developed so far. Using the methods described in this chapter, almost every substitution pattern on Trp is in theory synthesizable. The choice of method can be based on several aspects.

The procedures based on C–C couplings (chapter 2) enable the synthesis of complicated substitution patterns but require the synthesis of appropriately substituted indoles and protected precursors. These procedures are tolerant to several different functional groups. However, they only enable the synthesis of *C*- and *N*-protectedTrps and are not suited for the late-stage modification of peptides. The procedures based on indole synthesis (section 3) on the other hand, are suited for the installation of indoles in the sidechain of peptides and therefore enable, for example, the late-stage diversification of natural products. The methods based on C(sp^2)–H activation (section 4) can work on both protectedTrps or Trp-containing peptides. By using the appropriate protecting and directing groups, most positions on Trp can be accessed *via* C–H activation.

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