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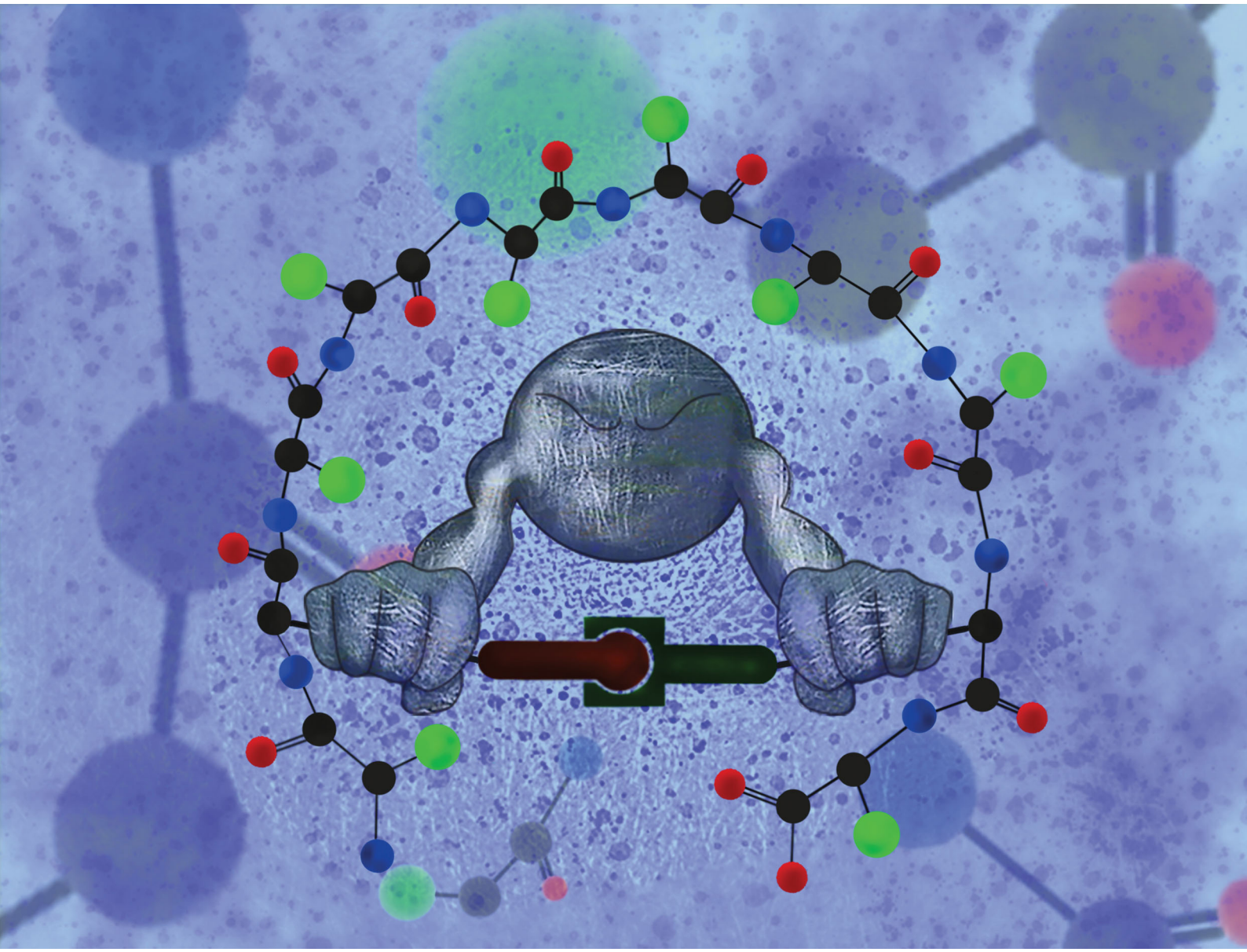

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Peptide macrocyclization by transition metal catalysis

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Peptide macrocyclization has traditionally relied on lactam, lactone and disulfide bond-forming reactions that aim at introducing conformational constraints into small peptide sequences. With the advent of ruthenium-catalyzed ring-closing metathesis and copper-catalyzed alkyne–azide cycloaddition, peptide chemists embraced transition metal catalysis as a powerful macrocyclization tool with relevant applications in chemical biological and peptide drug discovery. This article provides a comprehensive overview of the reactivity and methodological diversification of metal-catalyzed peptide macrocyclization as a special class of late-stage peptide derivatization method. We report the evolution from classic palladium-catalyzed cross-coupling approaches to more modern oxidative versions based on C–H activation, heteroatom alkylation/arylation and annulation processes, in which aspects such as chemoselectivity and diversity generation at the ring-closing moiety became dominant over the last years. The transit from early cycloadditions and alkyne couplings as ring-closing steps to very recent 3d metal-catalyzed macrocyclization methods is highlighted. Similarly, the new trends in decarboxylative radical macrocyclizations and the interplay between photoredox and transition metal catalysis are included. This review charts future perspectives in the field hoping to encourage further progress and applications, while bringing attention to the countless possibilities available by diversifying not only the metal, but also the reactivity modes and tactics to bring peptide functional groups together and produce structurally diverse macrocycles.

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Daniel G. Rivera graduated in Chemistry with first honors at the University of Havana in 2002. He earned the PhD in 2007 working on the development of multicomponent macrocyclization strategies in the group of Prof. L. A. Wessjohann. In 2008, he was appointed Head of Bioorganic Chemistry and in 2015 Director of the Center for Natural Products Research. His research interests focus on the synthesis of natural products, multicomponent and catalytic reactions, and peptide and protein chemistry. He is the President of the Latin-American Federation of Chemical Associations and currently, a Senior Visiting Scientist at KU Leuven.

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1. Introduction

The chemo- and regioselective conversion of a linear peptide into a macrocyclic scaffold has been a persistent and inspiring task for bioorganic chemists over the last two decades.[1–3] Two main driving forces have led the medicinal and biological chemists to focus on cyclic peptides:[4,5] the recognized pharmacological advantages of these macrocyclic molecules over their acyclic counterparts – evidenced in the often improved membrane permeability and metabolic resistance[4,6] – and the lower entropic cost upon binding to biological targets.[6,7] Besides those aspects intrinsically related to conformational constraints, there are two additional aspects prompting chemists to pursuit new peptide macrocyclization methods: (a) the need to undertake the macrocyclic ring closure in an orthogonal manner – ideally chemoselectively in presence of many unprotected side chains – and (b) the realization that the structural fragment (or linker) formed during macrocyclization might be key for the peptide bioactivity either by participating in the binding/transport processes[6,8] or by controlling the peptide conformation through steric restrains and/or intramolecular hydrogen bonding.[7,9]

While solid-phase peptide synthesis (SPPS) solved long ago the issue of orthogonality[10] and enabled lacton- and lactamization processes to be undertaken at specific, deprotected residues, the most effective and generalized methods for chemoselective peptide macrocyclization and stapling have emerged as a result of the development in homogenous metal catalysis.[2,11,12] Consequently, this field is experiencing a shift from the classic modification of small molecules to the late-stage derivatization of peptides[12–14] and protein bioconjugation,[15,16] remarkably, even proving success in aqueous conditions.

And what about diversity generation? Traditionally, peptide cyclization methods have not been a way of introducing chemical diversity. Peptide coupling-based lactamization and disulfide bond formation dominated the field of peptide cyclization for almost 30 years,[17] but they *per se* are not diversity-generating approaches. With the advent of new generations of peptide pharmaceuticals,[18,19] the generation of diversity not only by variation of the amino acid sequence but both by expanding the macrocyclic conformational space and varying the nature of ring-forming linkages became a necessity. In our opinion, two main peptide macrocyclization strategies are gaining increasing popularity, one based on multicomponent reactions as ring-closing procedures[1,20] and another more general comprising metal-catalyzed processes[12,14,21] based on C–H activation, oxidative cross-couplings, heteroatom ligation, and radical reactions, among others. This latter group is proving capable to tackle the diversity generation issue by enabling effective macrocyclic ring closures based on arylation, olefination, alkynylation, and alkylation of peptide side chains and functionalized termini. Indeed, there are two winning horses in the realm of metal-catalyzed macrocyclizations[8,22,23] for biological applications: the ruthenium-catalyzed ring-closing metathesis (RCM) and the copper-catalyzed alkyne–azide cycloaddition (CuAAC). However, both processes have been extensively reviewed in recent years[1,2,8,11,22,23] and therefore, only the latest and conceptually different contributions will be included in this account.

This review describes the most recent endeavors to diversify peptide macrocyclization approaches based on transition metal catalysis, providing a historical perspective of the evolution from the early examples to the levels of sophistication reached today. We focus on how the discovery of new types of metal complex-based reactivity has enabled, and continues to enable, the rapid creation of skeletal diversity in macrocyclic ring formation, which can be either in the peptide backbone or *via* cross-linking the side chains (*i.e.* peptide stapling). However, we do not make much emphasis on complete catalytic cycles previously outlined elsewhere, but on key metalated intermediates enabling a better understanding of the ring-closing step. The review provides a very comprehensive outline of all transition metals employed for this purpose and the many different reactivity modes used either to catalyze the direct ring closure or to activate a peptide functional group for the subsequent ring closure.

Leslie Reguera

Leslie Reguera graduated in Chemistry with honors at the University of Havana in 2002. She conducted her doctoral work at both the Universidad Nacional Autónoma de México and the University of Havana, where she did the PhD defense in 2009 with the award to the 'Best PhD Thesis of the Year'. She has been Visiting Scientist at the National Polytechnic Institute of Mexico and at the Leipzig University, Germany. Currently, she is Associate Professor at the University of Havana. Her research interests focus on synthetic methods and the development of transition metal materials for catalysis and gas adsorption.

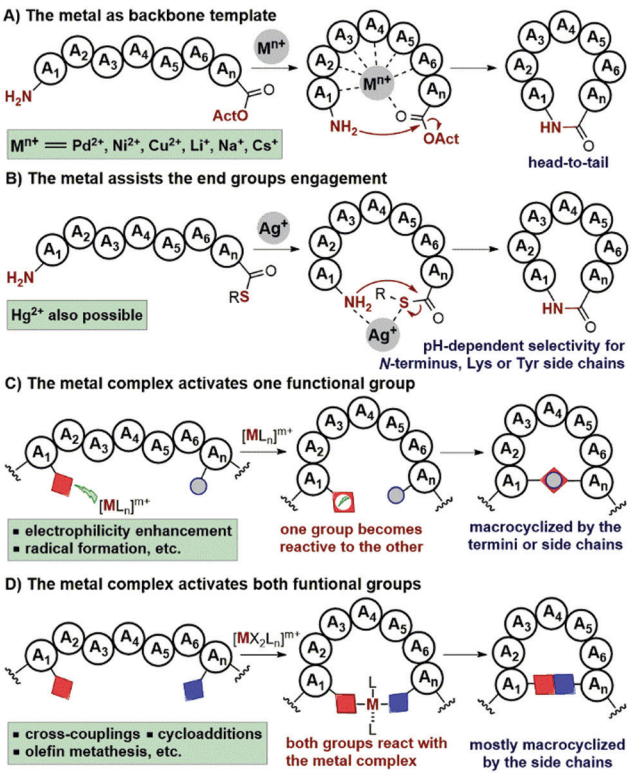
Erik V. Van der Eycken

Erik V. Van der Eycken is Full Prof. Organic Chemistry and Head of the Division of Molecular Design & Synthesis at KU Leuven. He received his PhD-degree (1987) in organic chemistry from the University of Ghent, Belgium. He spent time as visiting scientist at the University of Graz (2002) with Prof. C. O. Kappe, at The Scripps Research Institute (2003) in the group of K. B. Sharpless, and at Uppsala University (2004) with Prof. M. Larhed and Prof. A. Hallberg. The main focus of his research is the development of new synthetic methodologies in combination with enabling techniques.

2. Overview of peptide cyclization methods based on varied metal coordination modes

A general survey of all peptide cyclization methods relying on the utilization of metals reveals that they can be grouped in four different strategies, as depicted in Scheme 1, from which only C and D are actually metal-catalyzed processes. As the procedures included in strategies A and B have been previously outlined by Yudin and co-workers,[1] only a brief reference to such synthetic tactics will be given herein. In strategy A, the alkali- and transition metal coordination capacity of the amide oxygen atoms is utilized to allow the preorganization of the acyclic peptide in a circular conformation that helps to bring the two reactive ends closer each other. The ionophoric nature of several naturally occurring cyclic peptides is considered as the inspiration for this class of metal-templated macrocyclization.[1] Thus, the metal promotes the cyclization and avoids the use of extreme dilution conditions, but it rather acts as a template and not as a catalyst. The size of the metal may be a key factor to favor the cyclization of oligopeptides of different length.[24]

A second possibility is strategy B, which also utilizes a transition metal to facilitate the macrocyclic ring closure by bringing both termini closer to each other upon coordination of the N- and C-terminal groups with the metal. A successful example of head-to-tail and side chain-to-terminus macrocyclization was described with the use of peptide thioesters in the presence of Ag^{+} and Hg^{2+} (due to their high sulfur affinity) to assist the engagement of either the N-terminus, the Lys ε-amine or the Tyr phenolic group during a pH-dependent type of ring closure.[25] This approach also takes advantage of the entropic contribution provided by the complexation-mediated conformational preorganization, but the metal (used in excess) only assists and does not catalyze the peptide macrocyclization. This type of cyclization process might also take place under other, eventually more diluted conditions in the absence of the metal. Various examples of templated, assisted or promoted macrocyclization of (pseudo)peptides have been reported[26] and reviewed[1,17,27] elsewhere.



Scheme 1 Four different peptide macrocyclization strategies employing metals. (A) Metal-templated macrocyclization. (B) Metal-assisted or promoted macrocyclization. (C) Metal-catalyzed activation/macrocyclization sequence. (D) Metal-catalyzed macrocyclization.

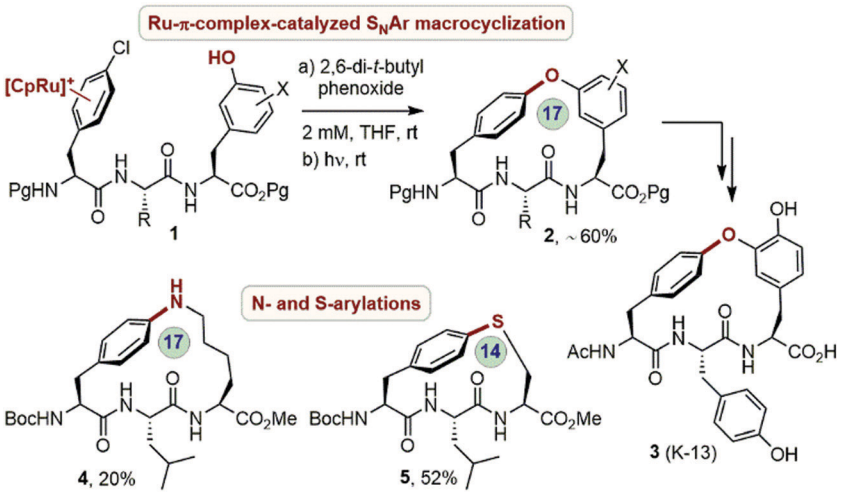
As shown in Scheme 1, strategy C outlines the cases in which a metal complex catalyzes the macrocyclization *via* activation of one peptide functional group, which thereby becomes reactive toward another functionalized side chain or backbone handle. To our knowledge, the first examples of this strategy were reported by the groups of Pearson[28,29] and Rich[30,31] in the 1990's, using S_NAr macrocyclizations of activated Ru–π-arene complexes. Originally, Pearson developed an Ullmann-type coupling based on the ability of a Ru–π-complex to enhance the electrophilicity of a chlorophenyl ring, thus making it suitable for a S_NAr reaction. The intermolecular coupling of a Ru–π-complex activated 4-chlorophenylalanine with 3-hydroxyphenylglycine proved to be effective without significant racemization, which led to the further adaptation to a macrocyclization protocol. As shown in Scheme 2, Rich and co-workers[30] implemented an intramolecular variant for the construction of the cyclic biaryl ether scaffold **2** similar to those found in the naturally occurring (glyco)peptides. In a series of parallel reports, Pearson undertook the Ru-catalyzed synthesis of a teicoplanin model cyclic peptide,[29] while Rich completed the total syntheses of the metallopeptidase inhibitors K-13 (**3**) and OF4949-III,[30] which all include the macrocyclic biaryl-ether motif. This Ru–π-arene activation strategy was later adapted to enable the heteroatom-arylation of other amino acid side chains, such as Lys (**4**) and Cys (**5**).[31]

The concept behind strategy C did not find generalization over the first decade of this century, although it has witnessed a renaissance in recent years with the utilization of decarboxylative radical reaction[32] and alkylation procedures as macrocyclization tools, which will be covered in the next sections. On the other hand, strategy D comprises the majority of metal-catalyzed macrocyclization methods reported, in which the transition metal binds the two reactive groups to enable the final C–C or C–heteroatom bond formation upon ring closure (Scheme 1D). Whereas the most relevant cases include the activation of – eventually non-proteinogenic – amino acid side chains, examples with reactive handles properly placed at the N- and C-terminus are also documented herein.

3. The quest for diversifying Pd-catalyzed peptide macrocyclizations

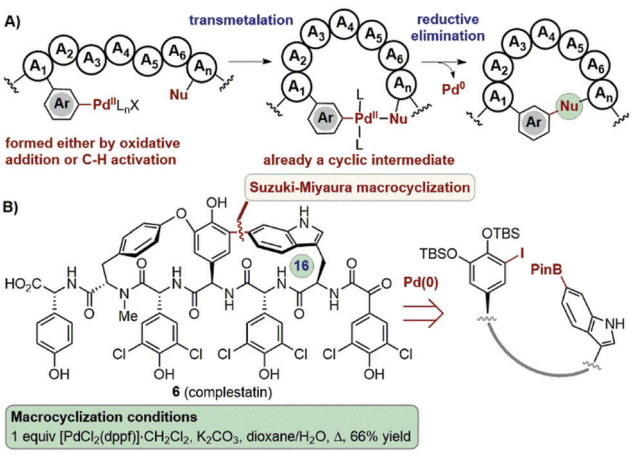
3.1. Learning from the pioneers: the Suzuki–Miyaura macrocyclization and beyond

Palladium complexes dominate the field of catalytic cross-couplings, including oxidative versions based on C–H activation



Scheme 2 S_NAr macrocyclization of peptide side chains *via* Ru–π-arene complex-catalyzed activation of phenyl groups.[29–31]

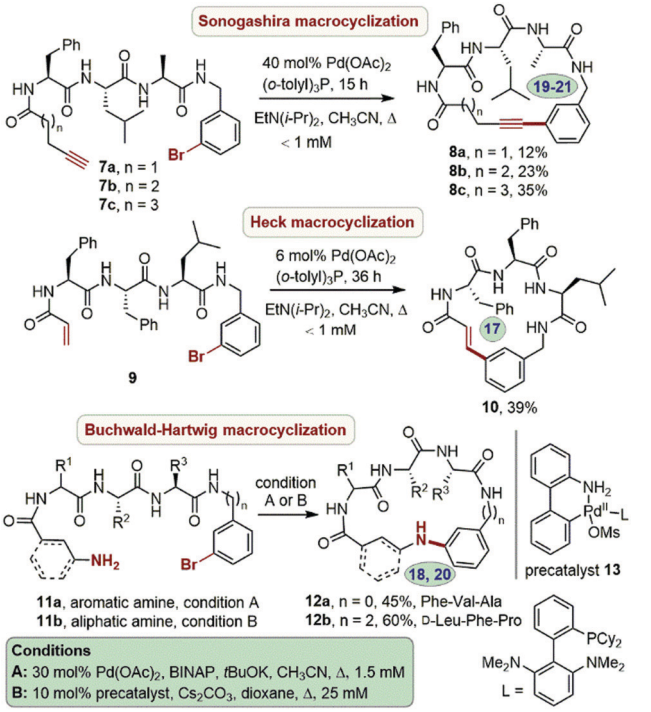
in which the high electrophilicity of the metal facilitates the palladation of C–H bonds.[21,33] This is also the case of transition metal-catalyzed macrocyclization processes, in which the greatest diversification of methods has emerged with the implementation of either Pd(0)- or Pd(II)-catalysis. Taking into account either of these latter catalytic cycles to exemplify macrocyclization strategy D depicted in Scheme 1, it is noticeable that the structural features of the peptide backbone are crucial to bringing together the aryl-Pd(II) intermediate and the nucleophilic counterpart (Nu, *e.g.* organometallic and boron compounds, alkene, alkyne, heteroatom, *etc.*) placed alongside the peptide sequence (Scheme 3A). In this regard, while the direct side-chain cross-coupling can be performed with peptides as short as three residues,[3,34] the success of peptide main-chain cyclization is biased by both the ring size and peptide capacity to fold into turn-like conformations. As shown in Scheme 3A, in such cross-coupling macrocyclizations, a key step is the transmetalation leading to the aryl-Pd(II)–Nu intermediate, which is already a cyclic species as both the aryl and nucleophile are tethered to the peptide chain. The final reductive elimination step releasing the cyclic peptide should be feasible if it does not add significant ring strain to the macrocyclic scaffold (*e.g.* going lower than a 12-membered ring).



Scheme 3 (A) Schematic representation of a peptide macrocyclization based on a Pd-catalyzed cross-coupling approach. (B) Use of the Suzuki–Miyaura reaction in the total synthesis of the cyclic peptide complestatin.[35]

Despite the fact that this review aims at highlighting the most recent trends in the field, it is worth highlighting the tremendous impact that the Suzuki–Miyaura and related cross-couplings have had in the site-selective derivatization of peptides and in the dawn of orthogonal Pd-catalyzed macrocyclization methods. A recent review[34] on the use of the Suzuki–Miyaura cross-coupling in peptide modification strategies covers most macrocyclization reports using this reaction, which will not be included herein. Nevertheless, Scheme 3B highlights a notable example described by Zhu's group on the successful utilization of this reaction to accomplish the ring-closing step of the biaryl macrocyclic fragment of the natural product complestatin (**6**).[35] More recent reports by Planas and Feliu extended the scope of this reaction to SPPS.[36]

Other Pd-catalyzed cross-couplings such the Sonogashira,[37,38] Heck,[39–42] Buchwald–Hartwig,[43,44] Stille[45] and Negishi[46] reactions have been also employed in peptide macrocyclization, with the group of Iqbal[38,42,43] providing various relevant examples. We chose to outline these results as they shed light onto the effect of the peptide structure on the ring-closing efficiency. Scheme 4 depicts the Sonogashira macrocyclization of tripeptide 7 having an alkyne and a bromophenyl handle at the N- and C-terminus, respectively. This Cu-free Sonogashira protocol was implemented with the peptide at extremely diluted conditions (<1 mM) and using a bulky, electron-rich phosphine ligand (L). The outcome proved that, under similar reaction conditions, the ring size determines the efficiency of this Pd-catalyzed ring-closing procedure, *i.e.*, the yield decreases from cyclic peptide **8c** (21-membered ring) to the smaller ones **8b** and **8a** (20 and 19-membered rings, respectively). In this sense, without the presence of a turn-inducing moiety (*e.g.*, Pro, an *N*-methyl or D-amino acid) and because the all-L-nature of acyclic precursors



Scheme 4 Pd-Catalyzed peptide macrocyclizations using Sonogashira, Heck and Buchwald–Hartwig cross-coupling reactions.[37,42–44]

7a–c, the shorter the sequence the more difficult is to bring together the two reactive ends during the transmetalation step. Accordingly, the greater degree of flexibility provided by the increasing length of the aliphatic alkyne tether in **7a–c** facilitates the formation of the cyclic alkyne–Pd(II)-aryl intermediate and its reductive elimination towards the rigid, linear alkynylbenzene linkage in product **8**.

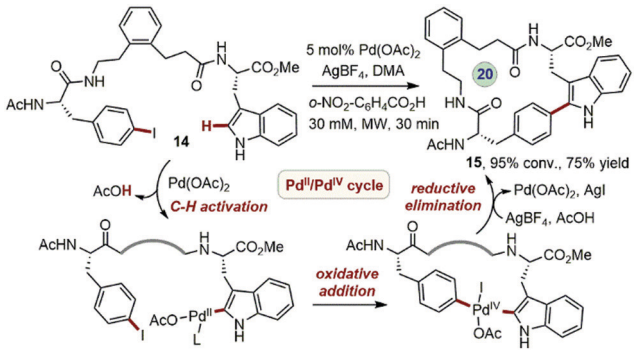
A similar tendency was found by Iqbal and co-workers in the Heck macrocyclization[42] of tripeptide **9** to render macrocycle **10** in moderate yield (Scheme 4). Despite the last step of the Heck reaction is a β-*syn* elimination instead of a reductive elimination, the feasibility of the formation of the cyclic palladated intermediate is already biased by the peptide sequence and the possibility to engage the two reactive ends.

Shortly thereafter, the same group developed a Buchwald–Hartwig peptide macrocyclization protocol by placing aniline and bromophenyl handles at the main chain.[43] As illustrated in Scheme 4, the use of standard Buchwald–Hartwig conditions with $Pd(OAc)_2$ and the 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP) ligand afforded the desired biphenylamine cyclic peptide **12a** in moderate yield. Hopkins and Sciammetta took advantage of the great progress achieved in the development of new ligands for the implementation of a Buchwald–Hartwig macrocyclization of aliphatic amines to C-terminal bromophenyl handles.[44] These authors took into account the favorable effect on the cyclization efficiency of peptide **11b** resulting from the incorporation of a Pro and a D-amino acid in its sequence (Scheme 4). Bromophenyl handles with aliphatic tethers of varied length were used to address the ring size effect in the cyclization yield. Interestingly, this Pd(0)-catalyzed macroamination reaction did not work efficiently with the classic bidentate BINAP ligand, and it required the more complex catalyst **13**, yet including a commercially available ligand. More recently, the same group implemented a methodology consisting in an on-resin catalytic *N*-arylation step followed by macrolactamization, thus rendering a combinatorial library of hybrid peptidic macrocycles for evaluation of their permeability properties.[47]

3.2. Macrocyclizations based on C–H activation

Thus far, most Pd-catalyzed peptide arylation methods described up to the first decade of this century were based on the classic use of halogenated aromatic amino acids and either organometallic[46,47] or boronic acid[34] species as nucleophilic counterparts. However, with the progress achieved in the field of C–H activation, a completely new venue of possibilities was opened to enable the direct arylation of native (otherwise unreactive) amino acid side chains.[14,21] One of the driving forces leading to the prompt implementation of C–H activation methods was the frequent incompatibility – with few exceptions[47] – of oligopeptides with C-nucleophiles such as organozinc and Grignard reagents. Another key issue when considering a complex peptide structure is the pursuit of a site-selective C–H activation process. As outlined in this section, the intrinsic differences in nucleophilicity of varied carbon centers, the increment of the acidity of a specific C–H bond, and the use of directing groups[48] (DG) has enabled to achieve impressive degrees of chemo- and regioselectivity in Pd-catalyzed peptide macrocyclizations.

3.2.1. C(sp^2)–H macrocyclizations. Based on reports of the direct arylation of indole,[49] Albericio, Lavilla and co-workers recognized the potential of exploiting C–H activation methods in a deprotected tryptophan (Trp) side chain,[50] since the unique nature and low abundance of this amino acid would enable site-selective peptide/protein derivatizations. The experimental conditions set for the chemoselective C-2 indole arylation of Trp-containing peptides included the use of catalytic $Pd(OAc)_2$, 1.5 equiv of a carboxylic acid additive and 1 equiv of $AgBF_4$. Microwave irradiation and 4 equiv of the aryl iodides proved efficient in the selective arylation of Trp, even in aqueous buffer, in the presence of other nucleophilic side chains such as those of Arg, Ser and Lys, but sulfur-containing residues were not compatible. The first adaptation of this method to a macrocyclization approach was reported by James and co-workers[51] shortly after its initial report. These authors implemented the macrocyclo-arylation of pseudo-peptides bearing an iodo-Phe connected to Trp by aliphatic and aromatic linkers. Scheme 5 depicts the macrocyclization of compound **14** to furnish macrocyclic pseudo-peptide **15** in a high conversion and isolated yield, for a process conduced at 30 mM concentration.[51] This reaction is suggested to proceed through a Pd(II)/Pd(IV) cycle, in which the palladation of the C-2 position of the indole is followed by oxidative addition to form a cyclic intermediate that undergoes reductive elimination to provide the side chain cross-linked peptide, releasing Pd(II). This and other Trp arylation methods – not necessarily based on Pd catalysis – have been recently reviewed by Ackermann and co-workers,[14] and may proceed by different mechanisms. For example, the



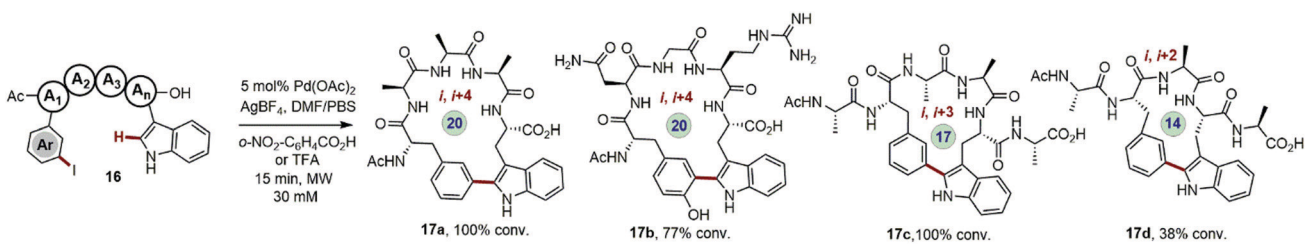
Scheme 5 Pd(II)-Catalyzed peptide macrocyclizations *via* Pd(II)/Pd(IV) cycle including the C(sp^2)–H activation of the Trp side chain.[51]

use of a boronic acid as arylating agent involves a Pd(II)/Pd(0) cycle, since after indole palladation by Pd(II) the aryl group is inserted by transmetalation. This latter comprises the formation of an aryl-Pd(II)–indole intermediate, that next undergoes reductive elimination to release Pd(0), which needs to be reoxidized to enter the catalytic cycle.[14] Therefore, this type of C–H activation process is flexible for Pd(II)/Pd(0) and Pd(II)/Pd(IV) catalytic cycles.

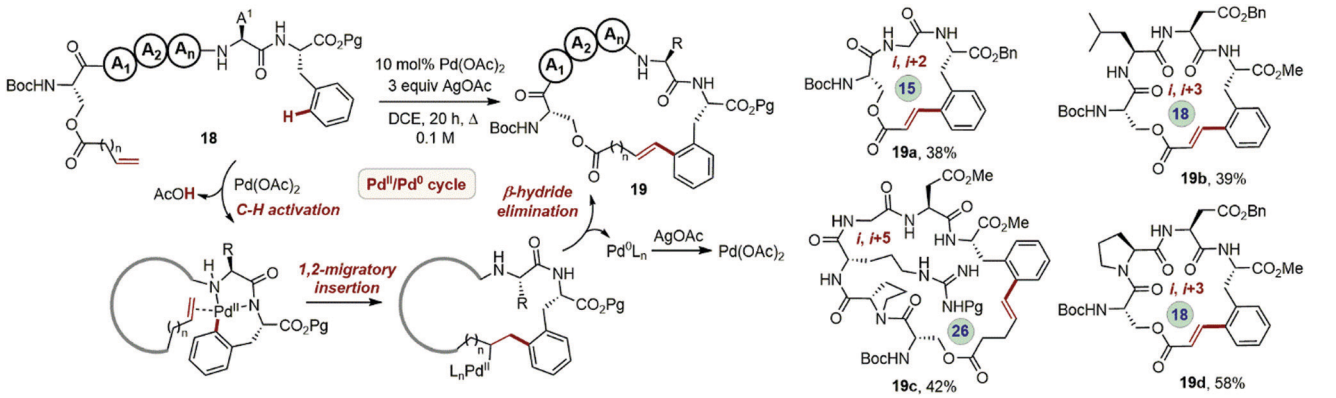
In 2015, Albericio, Lavilla and co-workers further expanded the scope of their protocol by developing the first actual, peptide stapling approach based on C(sp^2)–H activation.[52] The goal of peptide stapling (*i.e.*, side chain-to-side chain tethering) is to lock short peptides into specific, preferably bioactive conformations, for which the rigid biaryl connectivity was seen as highly promising. An in-depth analysis was conducted by the authors to address the influence of the sequence and distance between the Trp and iodo-Tyr or Phe residue in the Pd-catalyzed stapling. As shown in Scheme 6, the macrocyclization of all-L-peptides bearing Trp and iodo-Phe/Tyr placed at *i*, *i* + 4 and *i*, *i* + 3 positions proved effective for producing the biaryl stapled peptides **17a** and **17c**, respectively, in 100% conversion after short reaction time. However, the use of amino acid residues other than Ala partially dropped the conversion, as seen for compound **17b**. Notably, reducing the distance of the two reacting residues to *i*, *i* + 2 positions (*i.e.*, only one amino acid in-between) led to a significant decrease in the conversion to form peptide **17d**, for which the ring strain seems to be too high to enable an efficient ring closure. Although not shown herein, the authors proved that attempts to cyclize short peptides with the Trp and iodo-Phe in consecutive positions only led to the formation of the cyclodimeric product.[53] This confirms that, regardless of how efficient a metal-catalyzed process is, both the ring size and the peptide conformation are crucial for the success or failure of the macrocyclization. Nonetheless, if such structural considerations are taken into account, this Pd-catalyzed method is well suited for producing very complex, cell permeable macro(multi)cyclic peptides, as proven by Albericio, Lavilla and co-workers in their seminal report.[52] In this last example, and in other works covered by this review, isolated yields were not provided in the original publication and only the percentage of conversion (relative to the starting material) into the desired macrocycle was included for a set of compounds. In this sense, the percentages included in the different schemes refer to the isolated yields, unless otherwise identified with the conversion abbreviation (conv.); in this case the percentage refers to the conversion into the desired product.

3.2.2. C(sp^2)–H macrocyclizations *via* oxidative cross-coupling. Whereas the advent of C(sp^2)–H activation methods eliminated to some extend the need of using a boronic acid or organometallic reagents as C-nucleophiles in a cross-coupling process, to our knowledge, until 2018 all Pd-catalyzed macrocyclizations were still based on the employment of aryl halides as the electrophilic reagent required for the catalytic cycle. In the last two years, Wang's group has provided impressive examples of peptide macrocyclizations[54–56] based on Pd-catalyzed oxidative cross-couplings that include C(sp^2)–H activation steps. An oxidative cross-coupling is a process in which, instead of a reaction between a nucleophile and an electrophile, two nucleophiles (*e.g.* two hydrocarbons) react *via* metal catalysis and the participation of an external oxidant.[33,57] In peptide chemistry, this concept acquires marked importance due to the possibility of avoiding the prefunctionlization of amino acids, usually done by incorporation of halides and organoboron groups. Despite this field has witnessed one of the fastest growing in recent organic synthesis, the applications in the field of macrocyclization chemistry are just emerging.

One of the most common types of Pd-catalyzed oxidative cross-coupling is the arene–alkene coupling based on the activation of, at least, one C(sp^2)–H bond. Very recently, Wang and co-workers developed a series of C(sp^2)–H macrocyclization methods comprising an oxidative version of a Heck macrocyclization,[54] in which peptides bearing non-functionalized aryl handles cyclize with olefins *via* a Pd(II)/Pd(0) catalytic cycle. As depicted in Scheme 7, the first report of this series comprised the Pd-catalyzed δ-C(sp^2)–H olefination of Phe using the peptide backbone as an internal directing group. Translation of the



Scheme 6 Pd(II)-Catalyzed peptide stapling *via* C(sp^2)–H activation of the Trp side chain.[52]



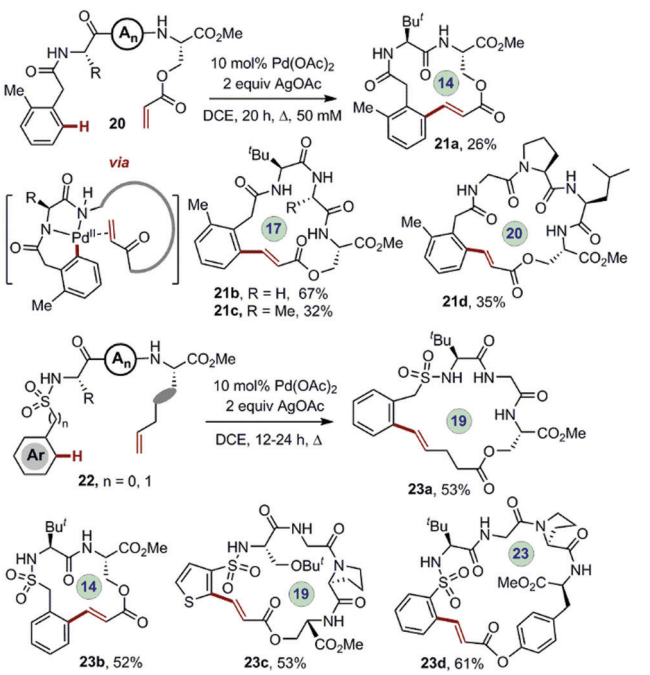
Scheme 7 Pd(II)-Catalyzed peptide stapling *via* δ-C(sp^2)–H macrocyclo-olefination of the Phe side chain. L_n refers to *n* ligands L, which are not necessary of the same nature.[54]

intermolecular version to a peptide stapling approach comprised the cross-linking of Phe and allylated Ser residues separated alongside the peptide sequence. Intermolecular experiments proved that site-selective *ortho*-olefination of the Phe residue takes places only when this amino acid has at least an additional residue in the N-terminal direction. This suggests that two amide bonds participate in the δ-C(sp^2)–H activation of Phe, forming a bidentate palladacycle intermediate including six- and five-membered rings.

As shown in Scheme 7, peptides of the general structure **18** with the reactive amino acids separated by 1–4 residues, underwent macrocyclization *via* a Pd(II)/Pd(0) catalytic cycle initiated by activation of the Phe δ-C(sp^2)–H bond. After C(sp^2)–H activation mediated by the amide directing groups, the catalytic cycle features a Heck reaction mechanism in which the 1,2-migratory insertion is followed by β-hydride elimination to give rise to the alkene-aryl cross-linked cyclic peptide. In this case, AgOAc is required as oxidant to regenerate Pd(II) and re-initiate the catalytic cycle. This process rendered stapled peptides, exemplified by **19a–d**, in moderate to very good isolated yields. As before, the efficiency of the macrocyclization procedure was influenced by the peptide sequence, albeit in this case not by the ring size. Thus, there was no significant difference in the cyclization of peptides with the Phe and the allylated Ser placed at *i*, *i* + 2 (**19a**), *i*, *i* + 3 (**19b**) and by *i*, *i* + 5 (**19c**) positions, but the incorporation of a Pro midway the sequence increased the cyclization yield, likely due to the turn-inducing effect of this residue.

In 2019, Wang and co-workers added new variants to the repertoire of Pd(II)-catalyzed macrocyclo-olefination procedures by varying the position of the reactive functionalities and the nature of the directing groups.[56,57] For example, they were able to change the directionality of the cyclization process by placing an arylacetamide handle at the N-terminus and an allylated Ser separated one or more residues in the C-direction. As shown in Scheme 8, the macrocyclo-olefination of peptides of type **20** led to a small library of 14-, 17-, 19- and 20-membered peptide macrocycles **21a–d** *via* C(sp^2)–H activation of the arylacetamide moiety.[56] Although the type of participation of the amide bonds in the C–H activation process was not disclosed, the authors proved the need of, at least, a dipeptide backbone from N- to C-direction for the catalytic process to take place. Therefore, it is likely that the C–H activation of the arylacetamide *ortho*-position also comprises the formation of a bidentate palladacycle, as it has been suggested in other reports.[58] As proven by Wang and co-authors before,[54] this protocol is suitable for both activated (*e.g.* acrylates) and unactivated olefins, thus rendering moderate to good yields of cyclic peptides featuring the aryl-alkene cross-linkages either in the side chain-to-side chain or side chain-to-terminus variants.

Besides relying on the backbone amides, Wang and co-workers introduced the use of sulfonamides in the C–H activation process.[55] Scheme 8 highlights the macrocyclo-olefination of peptides of type **22** including a sulfonamide moiety either directly linked to the aryl group or with a methylene tether. The Pd(II)-catalyzed



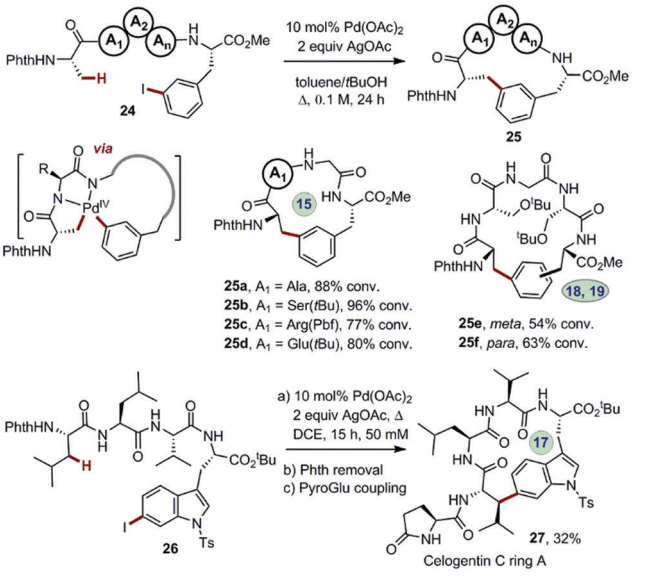
Scheme 8 Pd(II)-Catalyzed macrocyclo-olefination *via* C(sp^2)–H activation with the backbone amides and a sulfonamide as directing groups.[55,56]

cyclization conditions previously employed by this group enabled the construction of a diverse library of peptide macrocycles – exemplified by **23a–d** – with variation at the aryl moiety, the peptide sequence, the ring size and the type of olefin, *i.e.*, both activated (acrylate) and not. The authors proved by X-ray crystallography the direct participation of the sulfonamide group in the coordination of Pd(II) upon the activation of the aryl *ortho*-position.

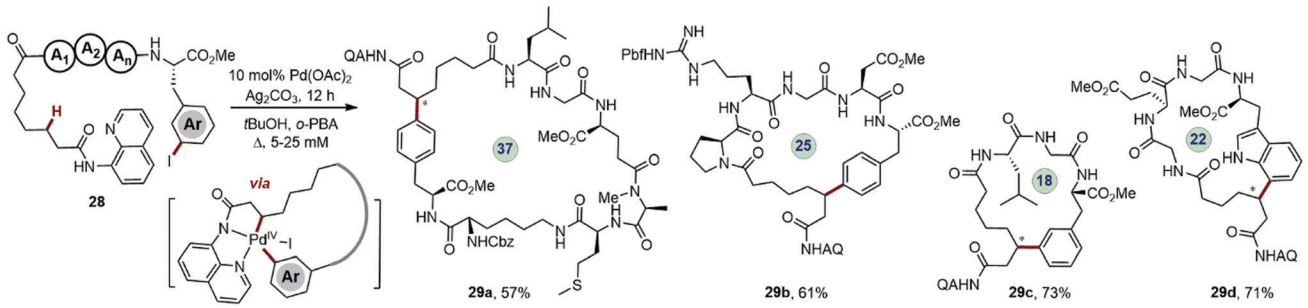
3.2.3. C(sp^3)–H macrocyclizations. The chemo- and regioselective arylation of aliphatic amino acids based on C(sp^3)–H activation methods date back to the beginning of this century, and such reports have been previously reviewed.[14,21] In these approaches, the role played by the directing group is crucial for the site-selective installation of an aryl or another moiety at β-, γ-, δ-, and ε-positions. In addition, the slight increase in the acidity of β-C(sp^3)–H bond of an amino acid by the installation of an *N*-phthaloyl (Phth) group also has a significant impact in the regioselectivity, mainly when seeking to target the N-terminal residue of a peptide in the presence of other aliphatic amino acids.[14,59] Such effective discrimination among several peptide C(sp^3)–H bonds is of great interest for macrocyclization purposes, as it would open an additional opportunity for peptide conformational constraint using the native aliphatic side chains. Based on previous knowledge in the Pd-catalyzed diversification of *N*-phthaloyl amino acids,[14,21] Yu's group was the first to achieve the β-C(sp^3)–H arylation and alkynylation of peptides at the N-terminal amino acid,[60,61] using the peptide backbone as directing group. These reports comprised a major advance in the late-stage peptide derivatization concept, and eventually encouraged research groups with expertise in macrocyclization chemistry to develop C(sp^3)–H peptide cyclization approaches.

In 2017, the groups of Albericio[62] and Wang[63] independently reported the application of Pd(II)-catalyzed β-C(sp^3)–H chemistry in peptide stapling strategies. As depicted in Scheme 9, the approach consisted of incorporating an iodo-Phe separated by a variable number of amino acids from the N-terminal *N*-Phth-Ala residue. Both groups implemented very similar reaction conditions, in terms of the amount of Pd(II) catalyst and oxidant, and obtained very similar results regarding the sequence and ring sizes that favor the catalytic ring closure. For example, the most successfully cyclized peptides of type **24** include a Gly or Pro in the sequences, providing the correct conformational bias for macrocyclization. Noisier, Albericio and co-workers addressed the possibility of cyclizing a peptide with only one Gly in-between *m*-iodo-Phe and *N*-Phth-Ala, but no conversion to cyclic peptide **25a** was obtained. Indeed, the 12-membered macrocyclic is too strained to be formed. However, stapled peptides with the *m*-iodo-Phe and *N*-Phth-Ala positioned at *i*, *i* + 3, *i*, *i* + 4 and *i*, *i* + 5 were obtained with good conversions, although in moderate isolated yields. Besides conducting a consistent variation of peptide sequences and lengths, both groups proved that the *p*-iodo-Phe could also be employed, but the macrocycle ring size needs to be large enough to accommodate such a linear and rigid phenyl spacer. The stapling procedure proved equally effective when conducted on-resin, which enabled the subsequent elongation of the peptide chain after an initial Pd-catalyzed cyclization.[62] Because of its relevance, we highlight the cyclization of peptide **26** conducted by Wang's group for the construction of ring A (**27**) of Celogenin C. This natural product had been previously synthesized by Feng and Chen[64] using an intermolecular β-C(sp^3)–H activation step to connect the Leu residue with the Trp indole moiety, albeit relying on the employment of the 8-aminoquinoline (AQ) directing group.

A collaboration of Chen's and other groups permitted the development of a C(sp^3)–H macrocyclization approach using iodo-aryl-containing peptides properly functionalized with an aliphatic linker capped with the AQ directing group.[65] Scheme 10 illustrates some of the complex and large macrocyclic pseudopeptides **29a–d** obtained by this powerful C–H activation protocol, which had been successfully exploited before for the derivatization of AQ-functionalized amino acids.[14] Besides the typical use of *m*- and *p*-iodo-Phe (**29a–c**), also 7-iodo-Trp (**29d**) and 4-iodobenzoyl Ser (not shown) residues were employed as electrophilic counterparts of the activated hydrocarbon nucleophile. The prochiral nature of the activated C(sp^3)–H bonds led to the formation of 1 : 1 diastereomeric mixture, albeit individual diastereomers could be separated and characterized. The use of relatively flexible substrates facilitated the Pd-catalyzed ring-closing step. Of note, a large macrocyclic peptide like that found in **29a** (37-membered ring) is rather difficult to obtain by any method, due to the entropic cost of bringing the reactive ends together in the absence of a favorable conformational bias. Certainly, the high efficiency of this procedure confirms the power of metal catalysis to achieve entropically demanding ring closures, as it takes advantage of the effective engagement of the two, otherwise faraway, functionalities around the metal center. On the other hand, small macrocycles with 11, 12, and 13-membered rings were also readily obtained, despite the fact that they are not strain-free due to the aromatic ring grafted within the cycle. X-ray analysis of some small macrocycles including a *p*-substituted phenyl moiety showed a bent aromatic ring due to the strain present in the cyclic scaffolds.[65]



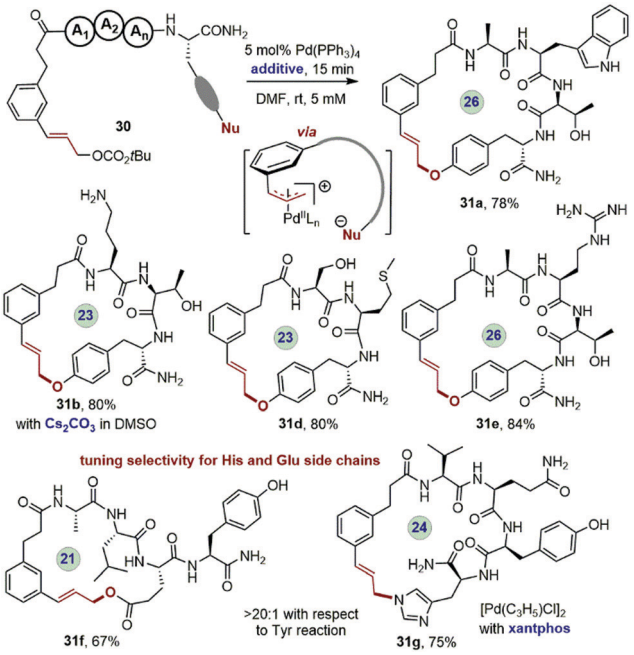
Scheme 9 Pd(II)-Catalyzed macrocyclization *via* β-C(sp^3)–H activation with the backbone amides as directing groups.[62,63]



Scheme 10 Pd(II)-Catalyzed macrocyclization *via* β-C(sp^3)–H activation with 8-amino-quinoline as directing group.[65]

3.3. Macrocyclo-allylation by Tsuji–Trost reaction

In an endeavor to provide chemoselective macrocyclization methods of unprotected peptides, Harran and co-workers[66] developed a macrocyclo-allylation method of amino acids side chains based on the Tsuji–Trost reaction.[67] This process comprises the Pd(0)-catalyzed nucleophilic substitution of allylic leaving groups *via* a Pd(II)–π-allyl complex acting as an electrophilic intermediate. The regio- and chemoselectivity of this reaction can be tuned depending on the ligand of choice and the reaction conditions.[68,69] As depicted in Scheme 11, Harran's work on peptide macrocyclo-allylation comprised the utilization of a common cinnamyl scaffold. Screening of a variety of reaction conditions and ligands enabled the chemoselective ring closure in highly functionalized unprotected peptides **30**.[66] Optimization of the reaction scope using $Pd(PPh_3)_4$ as catalyst led to a high isolated yield of macrocycle **31a** bearing a cinnamyl ether linkage. In this case, the phenol group of Tyr selectively behaved as nucleophilic counterpart without reaction of the threonine (Thr) and Trp side chains. The use of DMF/phosphate buffer 1 : 1 mixture at pH 7.4 and 8.5 also delivered high macrocyclization yield, confirming the positive effect of ion pairing in this type of Tsuji–Trost macrocyclization. Scheme 11 illustrates a putative intermediate comprising ion-pairing interactions between the cationic Pd(II)–π-allyl complex – *i.e.* the activated species – and an anionic nucleophile, suggesting that this is a type C macrocyclization strategy according to the representation given in Scheme 1. The ion-pairing phenomenon is well documented for the Tsuji–Trost reaction and its benefits in peptide macrocyclization have been also described,[1,20] mostly due to the proximity of both peptide termini previous to cyclization. Under the original conditions in DMF and $Pd(PPh_3)_4$ as catalyst, a variety of macrocycles were obtained in very good isolated yields due to the preferential reaction of the Tyr side chain over many others, including Met (**31d**), Arg (**31e**), Ser and Gln (not shown).



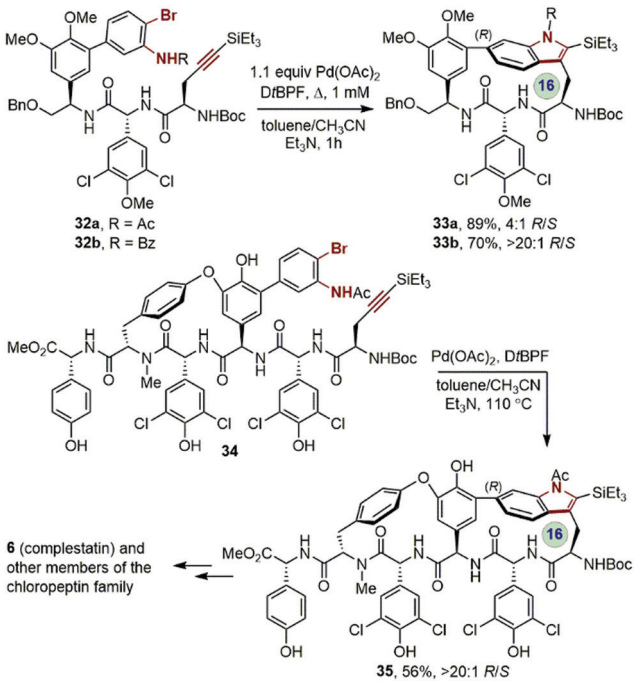
Scheme 11 Pd(0)-Catalyzed macrocyclo-allylation of peptide side chains by the Tsuji–Trost reaction.[66,68,69]

On the other hand, the chemoselectivity with such simple reaction conditions could not be reproduced with other peptides having free Lys/Orn, His and Glu side chains. For example, the synthesis of peptide macrocycle **31b** – including an Orn residue – was only possible with addition of Cs_2CO_3, confirming the relevance of favoring deprotonation of the phenol to keep the selectivity for Tyr in the presence of amino groups. For peptides having Glu/Asp side chains – which are more acidic than phenol – the standard conditions rendered only the allylic ester connectivity like in macrocycle **31f**, with no detectable reaction by the phenolic moiety. Once more, the addition of Cs_2CO_3 shifted the selectivity for the Tyr side chain, proving that in the presence of the two deprotonated side chains, the phenolate is preferred over the carboxylate nucleophile. Finally, the selectivity could be also tuned to favor the reaction of His side chain instead of Tyr. For this purpose, changing the catalytic system to $[Pd(C_3H_5)Cl]_2$/xantphos led to macrocycle **31g** with no perceptible reaction by the phenol. Alternatively, even with the same catalytic system, the macrocyclo-allylation of the phenol group was preferred over the imidazole upon addition of Cs_2CO_3. Such a fine-tuning in the bioorthogonality of the Tsuji–Trost peptide macrocyclization is a notable achievement of Harran's group,[66] as it may enable to boost the combinatorial production and screening of native peptide macrocycles.

3.4. Macrocyclization by Larock indole annulation

A series of papers from 2009 to 2013 by Boger and co-workers described what can be considered the first metal-catalyzed macrocyclo-annulation reaction.[70–72] In an effort to provide

an efficient approach towards the natural product complestatin (**6**) – different from those based on intramolecular Stille[73] and Suzuki–Miyaura[35] cross-couplings (see Scheme 3) – this group envisioned the utilization of the Pd(0)-catalyzed Larock indole synthesis[74] as a key step of their synthetic route. Initially, the focus was on the early construction of the functionalized, macrocyclic system **33** from the acyclic precursors **32** bearing an acylated bromoaniline moiety and a $SiEt_3$ substituted terminal alkyne.[70] After optimization, the chosen catalytic system was $Pd(OAc)_2$ in the presence of 1,1′-bis(di-*tert*-butylphosphino)-ferrocene (D*t*BPF) and triethylamine as base. As shown in Scheme 12, when the acyl group was acetate (**32a**), the selectivity was 4 : 1 favoring the natural (*R*)-atropisomer, while complete formation of this desired atropisomer was achieved with the larger benzoyl aniline substrate **32b**. The initial success using the Larock macrocyclization reaction with the simpler macrocyclic ring system **33** raised the question whether a good atropodiastereoselectivity could be achieved in a late-stage macrocyclization process with the whole peptidic structure **34** already assembled. Scheme 12 illustrates the successful generation of the macrobicyclic system **35** obtained as a single and natural (*R*)-atropisomer, which allowed for completing complestatin (**6**, also known as chloropeptin II) synthesis in just a few more steps. This result comprises that the left-hand cyclic moiety exerts a stereochemical control over the indole annulation step, even when the acetylated bromoaniline substrate **34** was employed. This key Pd(0)-catalyzed macrocyclization also proved to be highly chemoselective, as it could be carried out in good yield with precursor **34** bearing three phenols, four secondary amides, a carbamate, and four aryl chlorides.[71] Such an achievement paved the way for further reports by Boger's group on the synthesis of other members of the chloropeptin family and related tryptophan-derived cyclic peptides,[71,72] in which the indole moiety is grafted in the macrocyclic core.

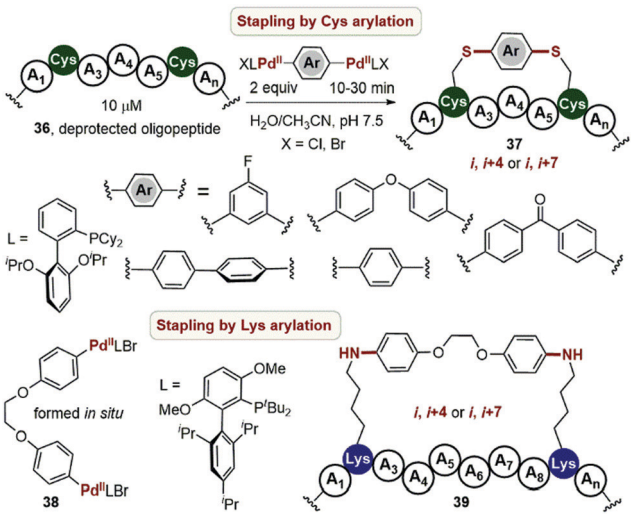


Scheme 12 Pd(0)-Catalyzed Larock macrocyclization in the synthesis of macrocyclic natural product peptides.[70,71]

3.5. Peptide stapling by Lys and Cys side chain arylation

The chemoselective heteroatom-arylation of native peptides and proteins is a field of continuing growth due to the potential applications of such bioconjugation approaches in chemical biology and immunology. Despite several recent reviews highlight the methodological development of such transition metal-catalyzed processes,[16,75,76] one specific arylation method[15] established by the groups of the Buchwald and Pentelute has been successfully translated to a peptide stapling protocol. As mentioned above, peptide stapling is a synthetic tool in which the side chains of two amino acid residues are cross-linked to render a conformationally constrained peptide, usually in α-helical conformation. In 2015, Buchwald, Pentelute, and co-workers reported Pd(II)-organometallic complexes that are effective for the chemoselective Cys arylation under biocompatible reaction conditions.[77] These Pd(II)-complexes, that include biaryl phosphine ligands, are available in high yield from aryl halide or trifluoromethanesulfonate precursors. They are also storable and air-stable, and some even incorporate water-soluble sulfonated biaryl phosphine ligands to enable Cys arylation in fully aqueous conditions.[78] As shown in Scheme 13, the utilization of these organometallic complexes in peptide stapling comprises the treatment of a fully deprotected oligopeptide **36** with the bispalladium aryl reagent to selectively cross-link two Cys side chains placed either at *i*, *i* + 4 or *i*, *i* + 7 positions. After the first report using the benzophenone linker,[77] this group extended the methodology to the introduction of a diverse array of aryl and bi-aryl linkers in peptide **37**, which proved to have a marked influence on the hydrophobicity, on the binding affinity to a specific target and on other biological properties.[79]

In an endeavor to extend the chemoselective arylation method to conjugation and stapling by the Lys ε-amine, Buchwald, Pentelute



Scheme 13 Peptide stapling by Cys and Lys arylation reactions.[78–81]

and co-workers studied more elaborated ligands seeking to facilitate the desired C–N reductive elimination.[80] Scheme 13 depicts the ligand present in the Pd(II) complexes chosen for Lys arylation, which required organic solvent (DMSO) and NaOPh as a weak base. This system proved chemoselective for Lys in the presence of other nucleophilic side chains as those of Ser, Tyr, Met, His, Trp, and Asn. However, Cys proved to react faster than Lys under these conditions and Arg also competed with Lys. For stapling purposes, a bispalladium biaryl reagent **38**, having an ethylene glycol tether, was generated *in situ* and reacted with deprotected oligopeptides (not containing Cys) to furnish stapled peptide of type **39**, which may have the two Lys either at *i*, *i* + 4 or *i*, *i* + 7 positions. In this case, protection of the N-terminus was required to avoid the competing reaction by that amino group. In general, it has been proposed that this class of two-component stapling resting on the use of bifunctional peptides and linkers is more versatile than the classic side chain cross-linkage.[8] The reason for this is that it usually offers better possibilities for fine-tuning the activity and the pharmacological properties through the parallel variation of the linker using a single bioactive peptide sequence.

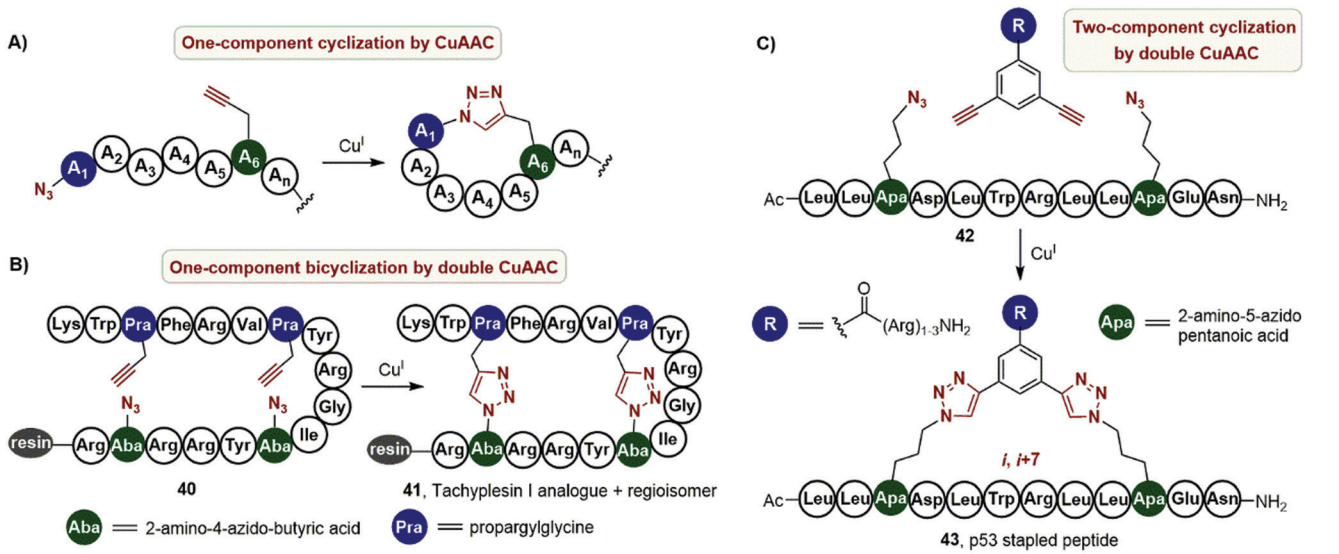
4. Cu-Catalyzed macrocyclizations get diverse in both methodological and reactivity terms

4.1. Methodological evolution of CuAAC in peptide macrocyclization

Shortly after the development of the click chemistry concept[81] with the dawn of CuAAC as a powerful synthetic tool,[82,83] this process began to be employed with success in macrocyclization approaches. In one of the first two papers of CuAAC, Meldal and co-workers[84] already revealed the efficient formation of novel peptide–triazole hybrid structures; so adaptations of this reaction to peptide macrocyclization either by one of the two termini[85–90] or by the side chains[2,91–95] have been frequent in the last two decades. Such approaches had very diverse purposes, including the access to turn[89,90] and helical secondary[91–94] structures as well as to complex macrocyclic architectures featuring chimeric peptide–triazole–steroid scaffolds.[96] However, they all followed the same methodological tactic of using a peptide bearing both the azide and the alkyne functionalities, either in the side chains or the termini. Scheme 14A depicts this type of 'classic' cyclization method in which a peptide bearing the two counter-reactive groups cyclizes in the presence of Cu(I), a process that can be undertaken either on solid phase[97] or in solution.

In 2011, Meldal and co-workers reported a macrocyclization approach based on a double CuAAC,[98] which comprised a significant advance in terms of secondary structure stabilization by the construction of triazole linkages as surrogates of disulfide bridges. Previously, double CuAAC cyclizations had been obtained either in short sequences or in peptides linked to resins, for which the cyclodimerization process was preferred over the Cu(I)-catalyzed ring closure. As shown in Scheme 14B, Meldal's methodology comprised the solid-phase assembly of peptide **40**, having the 17-residue sequence of bicyclic peptide Tachyplesin I, but incorporating propargylglycine (Pra) as replacement of Cys-3 and Cys-7 and azide-containing amino acids as replacement of Cys-12 and Cys-16. An on-resin double CuAAC macrocyclization of the deprotected, resin-bound peptide rendered the desired analog of Tachyplesin I (**41**), but also the other regioisomer connecting positions 3 and 12 and 7 and 16, respectively. While this approach proved that triazole linkages may serve as surrogates of disulfide bridges for locking bioactive β-hairpin conformations,[98] it also revealed the difficulty for achieving regioselectivity in double CuAAC cyclization with peptides bearing more than a pair of counter-reactive functionalities in the side chains.

Finally, a third methodology developed by Spring and co-workers[2,99,100] has emerged as a very versatile one for cyclizing



Scheme 14 Evolution of peptide macrocyclization methodologies using CuAAC.[98–100]

peptide side chains in an orthogonal and highly efficient manner. This class of two-component stapling approach encompasses the double CuAAC of diazido-peptides with dialkynyl linkers that may include additional functionality, such as a peptidic chain, a fluorescent tag and a conjugation handle.[8] Scheme 14C depicts one of the various successful examples of Spring's group comprising the stapling of a p53-peptide sequence **42** by double CuAAC macrocyclization.[99] Due to the long and rigid nature of bis-triazole aryl bridge formed, this two-component stapling is very effective for α-helix stabilization by tethering residues at *i*, *i* + 7 positions in the peptide chain, so that the linker expands two turns of the α-helical peptide **43**. Besides serving as inhibitor of the P53–MDM2 interactions, stapled peptide **43** bears a functionalized linker with either one or various Arg residues aiming at enhancing the cell permeability of the cyclic construct. Today, this Cu-catalyzed stapling is a mature methodology that has been applied to diverse target protein–protein interactions.[8]

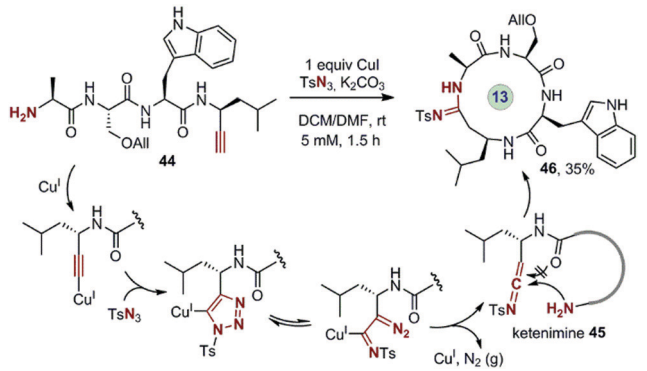
4.2. Cu-Catalyzed macrocyclizations with alkynyl peptides

The good availability of alkynyl amino acids and amines that can be incorporated into a peptide sequence in both solution and solid-phase approaches have made possible the diversification of Cu(I)-catalyzed peptide cyclization. This section outlines dissimilar macrocyclization processes that have been recently developed by exploiting various types of reactivity in Cu catalysis. As the CuAAC, they share the common characteristic of transiting *via* the formation of a Cu(I) acetylide intermediate, which may require the previous π-metal–alkyne complex activation to enable the proton abstraction.

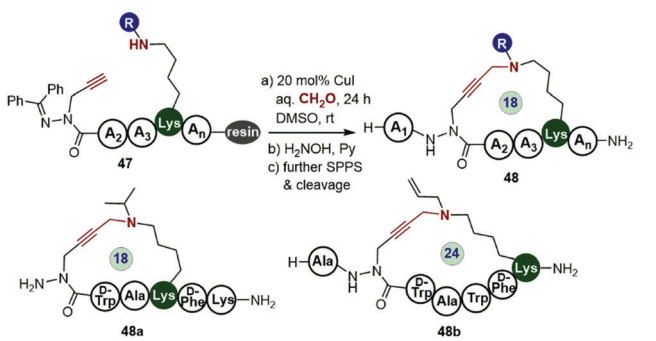
4.2.1. Denitrogenative macrocyclization. In 2014, Lin and co-workers developed a Cu(I)-catalyzed reaction of propargyl amides with tosylazide leading to enantiomerically enriched dihydropyrimidin-4-ones *via* the formation of a ketenimine intermediate that is trapped by the neighboring carbonyl group.[101] The ketenimine formation proceeds *via* CuAAC to render the Cu-triazole ring, which reopens to release dinitrogen leading to a ketenimine intermediate. The authors found out that this intermediate could be preferentially intercepted by the nucleophilic attack of an amino group of the same or a different peptide. As shown in Scheme 15, the implementation of the intramolecular version of this approach with alkynyl peptide **44** led to the development of a novel denitrogenative macrocyclization approach producing an internal β-amino acid with an amidine linkage.[102] Whereas the intermolecular variant – proceeding *via* the key ketenimine **45** – is typically completed within a few hours under mild reaction conditions, the macrocycle formation gave lower yields probably due to the short sequence that does not favor the intramolecular attack of the terminal amine. Nevertheless, the method enabled the preparation of two histone deacetylase inhibitor analogs consisting of a cyclic $\alpha_3\beta$-tetrapeptide skeleton like that of **46**.

4.2.2. The A^3-coupling macrocyclization. The transition metal-catalyzed reaction of a terminal alkyne, an aldehyde and an amine, known as the A^3-coupling, is a three-component process that has been applied in many different fields of organic and medicinal chemistry.[103] Being a multicomponent reaction, this convergent procedure generates high levels of complexity and diversity at the resulting propargyl amine with very low synthetic cost and using cheap catalysts such as Cu(I) species. In 2017, Ong, Lubell, and co-workers described the Cu(I)-catalyzed A^3-macrocyclization of peptides by tethering propargyl aza-residues and N^e-alkyl-Lys side chains.[104] As depicted in Scheme 16, the authors employed a solid-phase methodology comprising an on-resin A^3-macrocyclization of linear peptide **47**, followed by azapeptide deprotection and peptide sequence elongation to create of a parallel library of cyclic azapeptides of type **48**, analogs of GHRP-6 (His-D-Trp-Ala-Trp-D-Phe-Lys-NH_2). Variation of the sequence, the side chain tethering from *i*, *i* + 2 to *i*, *i* + 5 positions and the exo-cyclic moiety permitted the preparation of 15 macrocyclic azapeptides for biological screening. Remarkably, the aza-GHRP-6 cyclic peptide **48b** was found to exhibit the highest affinity for CD36 ever reported for a GHRP-6 analogue.[104]

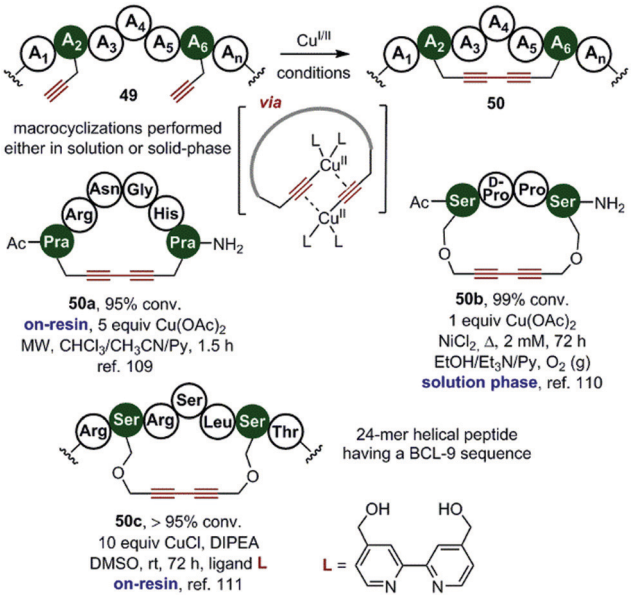
4.2.3. The Glaser macrocyclization. The Glaser oxidative coupling of two terminal alkynes under Cu catalysis is an old, text-book reaction[105] which, different from other Cu-catalyzed processes, had received little attention by the biomolecular chemistry community. The reason for this may be due to the use of strong amine bases, oxidants, high temperatures and varied additives, which along with the presence of Cu(I/II) salts results in the frequent degradation of complex biomolecules.[106] Although the original Glaser reaction was not universally



Scheme 15 Cu(I)-Catalyzed denitrogenative macrocyclization leading to cyclic $\alpha_3\beta$-tetrapeptides.[102]



Scheme 16 Cu(I)-Catalyzed A^3-macrocyclization leading to cyclic azapeptides.[104]



Scheme 17 Glaser macrocyclization leading to cyclic peptides constrained in β-turn and α-helical structures.[109–111]

applied in organic chemistry, various modifications such as those of Hay[107] and Eglington[108] led to synthetic improvements. Recently, this alkyne–alkyne coupling has found applications in bioconjugation chemistry[106] and peptide macrocyclization,[109–111] in which the rigid 1,3-diyne linkage has been devised for introducing conformational constraints during the ring-closing step. As shown in Scheme 17, this type of cyclization process requires the installation of two alkyne side chains in a linear peptide **49**, thus resulting in the formation of a diyne cross-linked peptide **50**. To our knowledge, the first example of a peptide Glaser macrocyclization was reported by Mallet and co-workers in 2014, using the Glaser–Eglington variant on propargylglycine (Pra) residues to access cyclic peptides of type **50a** featuring a β-turn structure.[109] The macrocyclization was achieved on-resin in high conversion using excess of $Cu(OAc)_2$ and pyridine ligand as optimized conditions. Intriguingly, the Glaser–Hay variant using CuCl and tetramethylenediamine as ligand did not work for this system.

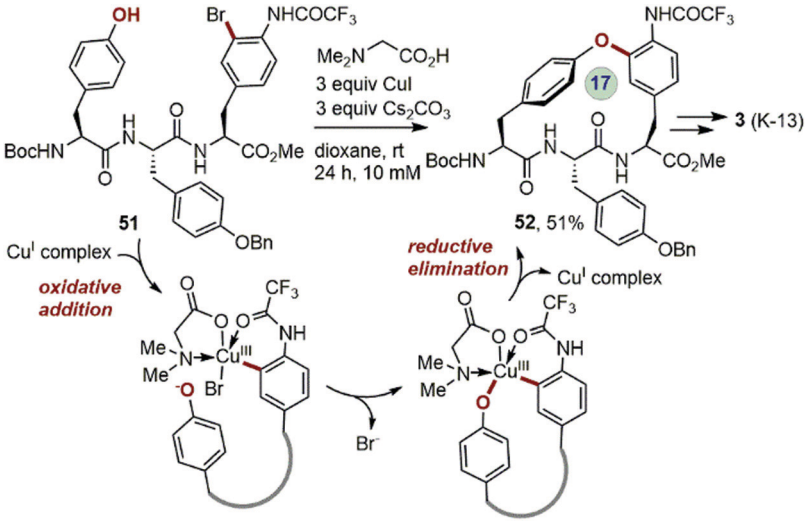
Later on, Verniest and co-workers[110] implemented in solution phase another variant of the Glaser–Hay macrocyclization of *O*-propargylated Ser and Tyr-containing peptides using the dual $Cu(OAc)_2$ and $NiCl_2$ catalytic system under O_2 atmosphere. Due to the short tetrapeptide sequences used by these authors, the central heterochiral D-Pro-L-Pro sequence had to be introduced to allow for the ring closure, leading to cyclic peptide **50b**. Although the mechanistic details of the dissimilar Glaser–Hay variants are still under debate, it is suggested that both the deprotonation and π-complexation of the alkyne with copper are crucial, while the reductive elimination from a bimetallic Cu(II) acetylide intermediate is mostly accepted as the final step.[112]

More recently, another Glaser macrocyclization protocol was reported by Dawson and co-workers,[111] based on their previous success in peptide and protein bioconjugation.[106] The authors implemented a solid-phase strategy including the on-resin peptide elongation and the Cu(I)-catalyzed macrocyclization of propargyl Ser. The alkyne side chains were cross-linked using CuCl, an essential bipyridine-diol ligand and DIPEA as base. The efficacy of this procedure was demonstrated in the synthesis at room temperature of BCL-9 (*i.e.*, a transcriptional activator of β-catenin) α-helical peptides of type **50c** in an excellent conversion. The Glaser stapling was conducted at positions *i*, *i* + 4, *i*, *i* + 5, *i*, *i* + 6, and *i*, *i* + 7 of a BCL9 peptide to address the influence of the alkyne side-chain tethering in the α-helical stabilization of the 24-mer model sequence. As expected, the higher α-helical content was found for the *i*, *i* + 4 and *i*, *i* + 7 connectivities, while *i*, *i* + 5, *i*, *i* + 6 showed more disordered structures since the side chains do not lie on the same face of the helix.[111] In addition, the *i*, *i* + 4 connectivity represents the optimal distance between the two side chains for expanding the 7 Å length of the resulting 1,3-diyne.

4.3. The Ullmann macrocyclization to biaryl ether cyclic peptide

The Cu(I)-catalyzed arylation of phenols with aryl halides is a process known as the Ullmann reaction. This type of *O*-arylation is of great synthetic relevance due to the wide occurrence of the resulting biaryl ether motif in natural products (see Section 2), but also because of the greater availability of Cu catalysts compared to other transition metals. However, for many years, the classical Ullmann procedures for biaryl ether formation required stoichiometric amounts of Cu reagents, high temperatures, and basic conditions, which limited the scope of the original transformation in peptide derivatization due to the risk of decomposition or racemization. Much effort has been devoted to the development of ligands and the elucidation of the reaction mechanism aiming at developing more efficient and milder Ullmann-type couplings.[113] Nonetheless, the translation of successful intermolecular Ullmann-type processes into macrocyclizations has remained underexploited as compared with other metal-catalyzed peptide cyclizations. In 2006, Ma and co-workers[114] discovered that the NHCOR group in 2-haloacetanilides was able to promote the Ullmann-type biaryl ether formation when *N*,*N*-dimethyl Gly was employed as ligand, thus enabling the Cu(I)-catalyzed reaction at room temperature and in high yield. The authors found a strong *ortho*-substituent effect on the Ullmann intermolecular coupling between 2-haloacetanilides and Tyr, which was next extended to a macrocyclization approach.

As shown in Scheme 18, the Ullmann macrocyclization of precursor **51** comprising the ring closure between the 2-bromotrifluoroacetanilide moiety and Tyr residue catalyzed by Cu(I), with *N*,*N*-dimethylglycine as ligand and Cs_2CO_3 as base, was achieved at room temperature. Cyclic peptide **52** was thus obtained in a suitable yield, enabling the total synthesis of the antitumor agent K-13 (**3**). The authors proposed a mechanism involving oxidative addition of the aryl bromide moiety to the Cu(I)-*N*,*N*-dimethylglycine complex to form a Cu(III) intermediate, which would then react with the nucleophilic phenoxide to deliver the biaryl ether moiety *via* reductive elimination, regenerating the Cu(I) complex.[114] Alternatively, more recent evidence[113] with this



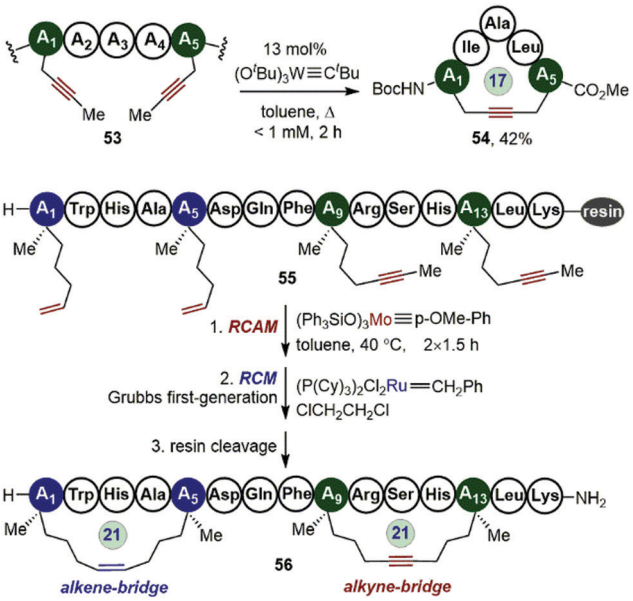
Scheme 18 Ullmann macrocyclization in the total synthesis of biaryl ether cyclic peptides.[114]

class of bidentate ligand suggests an alternative mechanism in which the Cu(I) complex would first add the anionic phenoxide ligand generating a tricoordinate anionic Cu(I) intermediate, followed by the oxidative addition of the aryl bromide moiety to form the pentacoordinate Cu(III) intermediate. In either case, both the chosen ligand and the stabilizing *ortho*-substituent effect seem to be crucial for the mild character of this approach compared to other Ullmann-type procedures.

5. Diversification of the transition metals and the reactivity-driven macrocyclizations

5.1. Ring-closing alkyne metathesis catalyzed by tungsten and molybdenum complexes

The original term peptide stapling was coined in 2000 by Verdine and co-workers for the utilization of ring-closing metathesis (RCM) in the synthesis of all-hydrocarbon bridged α-helical peptides.[115] It is known that the pioneering report of Blackwell and Grubbs on the use of Grubbs[116] catalysts for cross-linking two *O*-allyl-Ser side chains paved the way for the progress of this powerful technology. As an extension of the intramolecular metathesis concept, some groups have employed the ring-closing alkyne metathesis (RCAM) as a macrocyclization tool for the stabilization of peptide secondary structures. Although it had been used before in macrocyclization chemistry,[117] to the best of our knowledge the first report of RCAM peptide macrocyclization was made by Liskamp and co-workers in 2005.[118] The authors employed tungsten (W) complex-catalyzed RCAM to produce alkyne-bridged cyclic peptides mimicking the A-, B-, C-, and (D)E-ring system of the peptide antibiotic nisin Z. As depicted in Scheme 19, the strategy consisted in assembling peptides of type **53** with two alkyne-functionalized amino acids and utilizing the tungsten–alkylidyne complex $(t\mathrm{BuO})_3\mathrm{W}{\equiv}\mathrm{C}{-}t\mathrm{Bu}$ to cross-link the side chain *via* alkyne metathesis. Not only pentapeptide **54** was obtained in acceptable yield, but also a variety of alkyne-bridged macrocycles,



Scheme 19 Tungsten and molybdenum-catalyzed RCAM in the synthesis of cyclic peptides.[118,120]

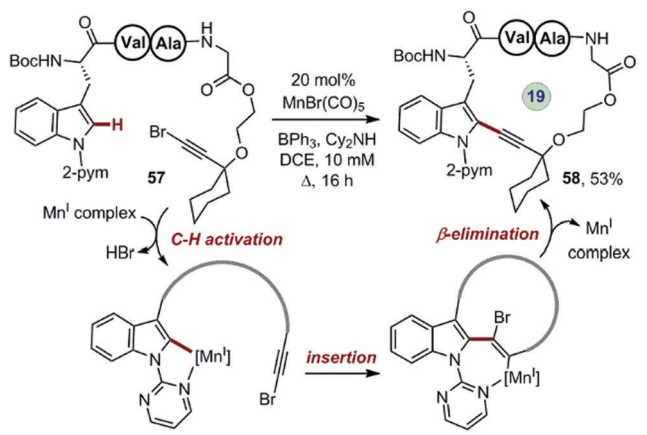
containing four to seven amino acid residues, were produced in moderate to good isolated yields using a solution-phase RCAM protocol. Alkyne-bridged cyclic peptides designed as vancomycin mimics have been also obtained by the same group.[119] An advantage of this procedure is the possibility of further derivatization either by reduction to the alkane, the *cis*- or *trans*-alkene or the use of the triple bond as a handle for subsequent modifications, such as electrophilic addition and cycloaddition reactions.[118]

Recently, Fürstner, Grossmann, Waldmann and co-workers[120] tackle the chemoselectivity issue in the field of ring-closing metathesis by developing an orthogonal approach in which peptides bearing two alkynes and two alkene functionalities could be sequentially cyclized by RCAM and RCM, respectively. Scheme 19 depicts the orthogonal on-resin macrocyclization

processes carried out for peptide **55** leading to bicyclic peptide **56**, which is endowed with an alkyne bridge between residues 9 and 13 and an alkene bridge between residues 1 and 5. The last generation molybdenum (Mo)-complex was chosen due to the chemical orthogonality of this RCAM with the Ru-catalyzed RCM, thus allowing to conduct the two processes in a sequential manner. Both placing of the reactive residues at i, $i + 4$ positions and employing α,α-disubstituted chiral amino acids (as proven by Verdine and co-workers[115]) aimed at achieving the α-helical stabilization of the resulting peptide **56**. This orthogonal RCM/RCAM strategy enabled the synthesis of bicyclic peptide inhibitors of the small GTPase Rab8, one of which showed the highest affinity ever reported for an activated Rab GTPase.[120]

5.2. Manganese-catalyzed macrocyclization based on C–H activation

Recent trends in the field of C–H activation are favoring the use of the inexpensive 3d metals to achieve chemoselective transformations that, before, were only possible with the use of precious transition metals such as palladium, gold, rhodium, ruthenium, *etc.*[121] The late-stage derivatization of Trp-containing peptides is one of the C–H activation processes in which manganese-catalysis has been able to reproduce synthetic modifications previously done with more costly 4d and 5d metals.[14] Ackermann's group has pioneered this field with seminal reports including the Mn(I)-catalyzed C-2 indole cyanation,[122] allylation[123,124] and alkynylation[125] of Trp, including the macrocyclization of Trp-containing skeletons. Scheme 20 depicts an example of peptide macrocyclo-alkynylation based on Mn(I)-catalyzed C–H activation using the indole-linked 2-pyrimidine moiety as directing group. Optimization of the intermolecular reaction showed that 1,2-dichloroethane (DCE) as solvent, an amine additive (dicyclohexyl amine), triphenylborane (BPh_3) as Lewis acid co-catalyst and 80 °C were the best conditions for this catalytic alkynylation using 5 mol% of the Mn-catalyst. However, the macrocyclization was conducted with 20 mol% of the Mn-catalyst and at 10 mM concentration of the alkynyl peptide, rendering macrocycle **58** in good yield for the complexity of this process.[124]



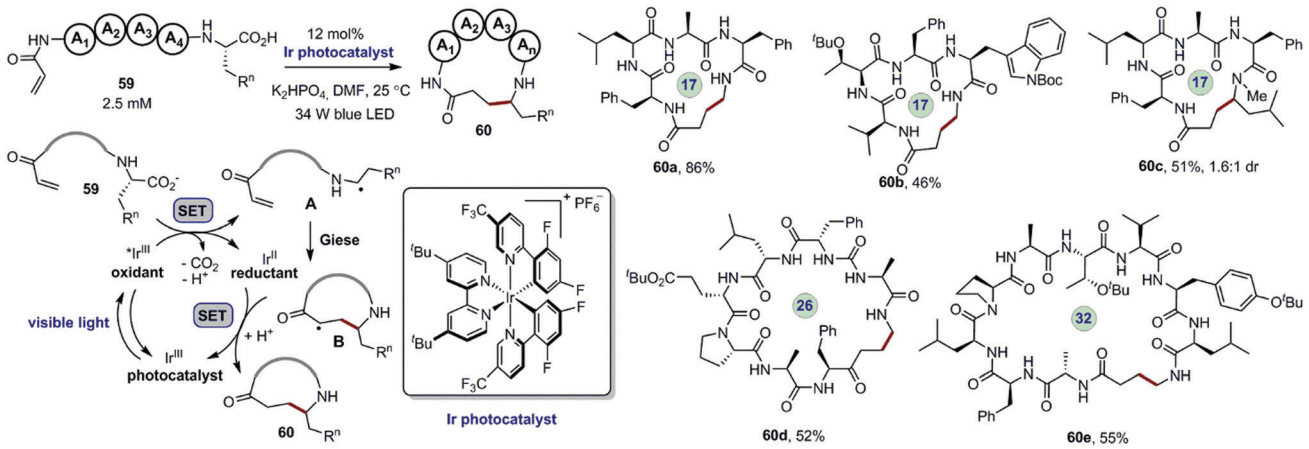
Scheme 20 Manganese-catalyzed macrocyclo-alkynylation of Trp-containing peptides.[124]

The mechanism proposed by the authors comprises the initial formation of a peptide–$Mn(CO)_4$ complex in which the directing pyrimidinyl indole moiety enables the proton abstraction at position 2 of indole. The intramolecular insertion of the alkynyl bromide leads to a seven-membered metallacycle with a macrocyclic tether between the indole and the resulting alkene moiety. As shown in Scheme 20, the final β-elimination and release of the Mn-catalyst regenerates the alkyne functionality linked to C-2 of the indole ring. It was proposed by the authors that the BPh_3 additive accelerates the crucial β-elimination. Besides cyclization, this method enabled the incorporation of a variety of biomolecular, fluorescent and functional handles to the indole moiety under racemization-free conditions and without affecting other Trp and Phe residues not bearing the pyrimidine directing group.[125]

5.3. Iridium- and nickel-catalyzed decarboxylation and Giese macrocyclization

During the last decade, the use of light-mediated catalysis has permitted the development of a wide variety of synthetic transformations under operationally simple conditions. The field of photo-redox catalysis has experienced a notable renaissance, with new activation modes and C–C bond-forming procedures frequently emerging and expanding the scope of synthetic methodologies and total synthesis approaches.[126,127] Whereas Ru-complexes and organic molecules have been widely employed as photocatalysts, iridium polypyridyl complexes have proven to have a broader synthetic scope, in spite of their high cost.[127] Recent progress in photocatalysis, mostly led by MacMillan's group, has also advanced the field of peptide and protein chemistry by providing novel macrocyclization[128,129] and site-selective conjugation[130] approaches over the last three years. In 2014, MacMillan and co-workers[131] developed an iridium-catalyzed photo-induced carboxylic acid oxidation procedure generating radical species that undergo 1,4-conjugate addition to Michael acceptors (Giese reaction). The mechanism comprises the photoredox-mediated CO_2 extrusion under mild conditions to generate primary, secondary, and tertiary radicals that subsequently participate in the radical conjugate addition. The authors proved that this oxidative decarboxylation pathway was also efficient with a variety of α-amino acids,[131] thus paving the way for the late-stage chemoselective modification of peptides, including macrocyclization.

As shown in Scheme 21, the decarboxylative radical macrocyclizations of peptides such as **59** were conducted under diluted conditions *via* the generation of a C(sp^3)-radical at the C-terminal residue[128] and the subsequent reaction with the N-terminal acryloyl acceptor. The selective C-terminal functionalization is possible due to the easy formation of radical species at an α-amino carboxylate through a single-electron transfer (SET) decarboxylation. The mechanism proposed comprises the visible-light irradiation of the Ir(III)-photocatalyst $Ir[dF(CF_3)ppy]_2(dtbbpy)^+$ to access the excited state $*Ir(III)^+$, which is a strong oxidant and enables the selective SET oxidation of the peptide carboxylate salt. The as-generated carboxyl radical undergoes CO_2 extrusion to render the stable, nucleophilic α-amino radical (**A**) that executes an intramolecular

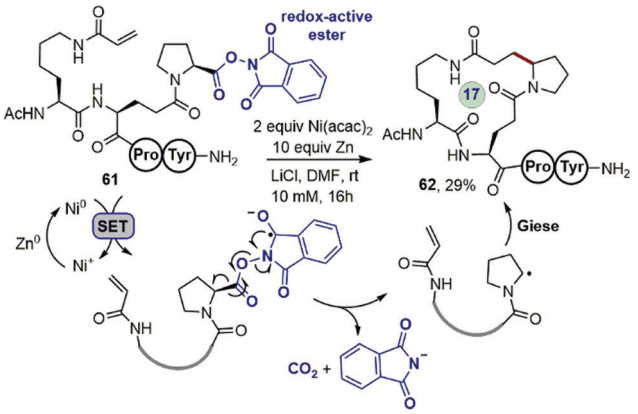


Scheme 21 Iridium-catalyzed photo-redox decarboxylation and Giese macrocyclization of *N*-acryloyl peptides.[128]

radical addition to the N-terminal acryloyl fragment, thus closing the macrocyclic ring. This Giese ring-closing step generates an electrophilic α-acyl radical (**B**) that performs a SET reduction to the macrocyclic enolate with regeneration of the cationic Ir(III)-complex to complete the photoredox catalytic cycle. Final protonation of the enolate delivers the desired macrocyclic peptide **60** in excellent conversion and good isolated yield. Selected compounds **60a–e** are shown in Scheme 21 as representative of the cyclopeptide library produced. The method proved to have a wide scope for peptides of varied ring sizes and side chain-protected amino acids, including the sequence of a Somatostatin receptor agonist. Nonetheless, poor diastereoselectivity was achieved when amino acids other than Gly were used at the C-terminus. This class of photo-redox process belongs to type C macrocyclization strategy (see Scheme 1), as the metal complex catalyzes the activation (radical formation) of one peptide terminus to allow the reaction with the other one (the conjugated olefin).

In parallel to MacMillan's photo-redox macrocyclization, Baran and co-workers[132] described a less costly and equally efficient variant of the decarboxylation/Giese macrocyclization approach based on Barton's radical chemistry.[133,134] The new method did not rely on the, also well-known, photochemical reactivity of active esters,[32] but on the redox character that makes them capable to accept electrons from nickel complexes *via* SET. This class of Ni-catalyzed reductive decarboxylation furnishes alkyl radicals capable to undergo varied reactions, including the Giese reaction.[32] Before tackling the challenge of peptide cyclization, an extensive optimization was conducted with dissimilar ligands, additive salts and reducing metals. The best conditions for the Ni-catalyzed radical formation were found with the use of *N*-hydroxyphthalimide (NHPI) esters, activated zinc for reducing Ni(II) to Ni(0) and LiCl as essential additive for the conjugate addition. A myriad of carboxylic acid secondary metabolites and active components (*e.g.* fatty and bile acids, terpenes, peptides, *etc.*), modified as redox-active ester, were subjected to Ni-catalyzed decarboxylation and Giese reaction as an efficient way of chemoselective derivatization.[132]

The authors also proved that N-terminal acryloyl peptides react well with amino acid-NHPI esters, even in the presence of

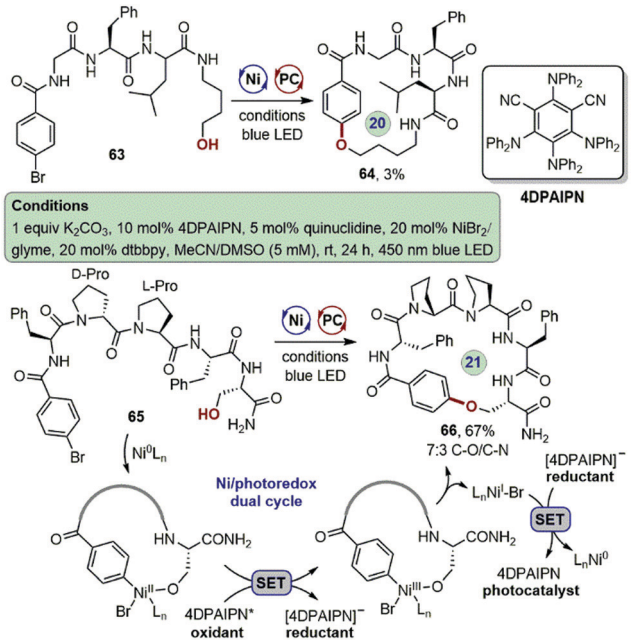


Scheme 22 Nickel-catalyzed peptide-active ester decarboxylation and Giese macrocyclization.[132]

allyl esters at Glu side chains, while NHPI ester-containing oligopeptides efficiently performed radical addition to conjugated olefins. As shown in Scheme 22, peptide **61** functionalized with both an *N*-acryloyl group and a NHPI ester at Lys and Glu side chains, respectively, underwent Ni-catalyzed decarboxylation and Giese macrocyclization to render cyclic peptide **62** in good isolated yield.[132] This protocol features great operational simplicity and inexpensive reagents, albeit it was only reported for Pro-NHPI esters without revealing if other amino acid esters could undergo the chemoselective radical macrocyclization so efficiently. In this sense, Baran's group has continued developing new carboxylic acid coupling reagents for accessing active esters suitable for decarboxylation processes under varied conditions.[32,135]

5.4. Dual nickel/photoredox-catalyzed macrocyclization

Based on the work of MacMillan's group on the Ni/photoredox-catalyzed C(sp^2)–O coupling,[136] Sciammetta and co-workers recently developed an interesting peptide macrocyclization procedure furnishing aryl ether connectivities.[129] The interplay between transition metal and photocatalysis, also referred to as metallaphotocatalysis, has proven notable efficacy for conducting non-traditional cross-coupling approaches,[126] including C(sp^3)–O



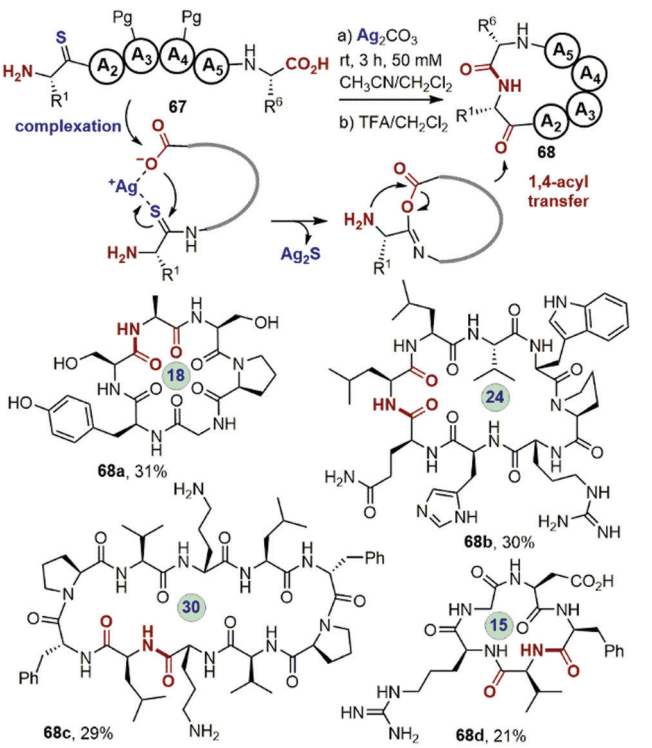
Scheme 23 Dual Ni/photoredox-catalyzed macrocyclization of N-terminal bromobenzoyl peptides functionalized with hydroxyl groups at the backbone or amino acids side chains.[129]

and C(sp^2)–O bond formation procedures. In this sense, nickel is known to engage well in SET and radical capture mechanisms,[137] which facilitates merging Ni catalysis with photoredox transformations mediated by visible-light irradiation of either iridium complexes or organic dyes. As shown in Scheme 23, Sciammetta's adaptation of the catalytic C(sp^2)–O coupling to peptide macrocyclization comprised the installation of a bromobenzoyl moiety at the N-terminus to enable the dual Ni/photoredox-catalyzed reaction with Ser (hydroxyl) and Tyr (phenol) side chains. Despite the fact that the original report by the MacMillan laboratory[136] also utilized Ir(III)-complexes to modulate the oxidation states of nickel *via* SET, Sciammetta's group found 1,3-dicyano-2,4,5,6-tetrakis(diphenylamino)-benzene (4DPAIPN) to be a better photocatalyst for executing the dual Ni/photoredox coupling of bromoaryl peptides and hydroxyl-functionalized amino-acid side chains.

A wide variety of intermolecular couplings were initially performed in moderate to good yields using simple bromobenzoyl dipeptides and several alcohol partners, including aliphatic ones, partially protected sugars and short peptides containing Ser, Thr and Tyr residues. However, in the case of macrocyclization, the incorporation of a long aliphatic alcohol chain at the C-terminus of peptide **63** led to a very low conversion to cyclic peptide **64**, probably due to the detrimental effect of the high conformational flexibility of the aliphatic fragment. In contrast, peptide **65**, bearing the turn inducer fragment D-Pro-L-Pro, reacts well under the same conditions to render cyclic peptide **66** in very good yield, albeit as a mixture resulting from the formation of the C–O and C–N (terminal carboxamide) connectivities.[129] The reaction mechanism comprises the oxidative addition of the bromoaryl peptide to the Ni(0) complex to furnish the Ni(II)L_n–aryl complex, which intramolecularly adds the side-chain hydroxyl group to give the cyclic Ni(II)L_n–aryl–alkoxide complex. A key aspect of this mechanism is the inability of this Ni(II) intermediate to undergo reductive elimination to form the C(sp^2)–O bond and release Ni(0). Instead, the Ni(II) complex undergoes photocatalytic oxidation to the Ni(III)L_n–aryl–alkoxide complex *via* SET in presence of blue LED irradiation, also leading to the reduction of activated 4DPAIPN. Thus, the above-mentioned Ni(III) complex is then capable to undertake reductive elimination to produce macrocyclic aryl-ether peptide and a Ni(I) complex, which is next reduced *via* SET to regenerate Ni(0) and the photoredox catalysts, restarting the dual Ni/photoredox cycle. Together with many other metal-catalyzed intermolecular couplings enabled by photoredox catalysis,[126] this macrocyclization protocol demonstrates the power of merging transition metal and photoredox chemistry, in which SET promotes crucial steps that are not viable without the redox process. This process provides an important alternative to classic peptide macroetherification protocols previously discussed, such as the Ullmann and Tsuji–Trost reactions, S_NAr and S_N2 displacements.

5.5. Silver-promoted macrocyclization of N-terminal thioamide peptides

One of the few methods featuring macrocyclization strategy type B (see Scheme 1) was reported in 1997 with the use of Ag^+ or Hg^{2+} to promote the cyclization of peptide thioesters.[25] A novel variant of such approach using a Ag(I)-promoted macrocyclization – also based on a complexation-mediated



Scheme 24 Ag(I)-Promoted macrocyclization of N-terminal thioamide peptides.[138]

conformational preorganization – was described in 2019 by Hutton for N-terminal thioamide peptides.[138] As shown in Scheme 24, the installation of a thioamide at the N-terminal residue in peptide **67** enables Ag(I) to coordinate the two termini while activating the thioamide towards the carboxylate nucleophilic attack, leading to the formation of a cyclic intermediate and releasing silver(I) sulfide. The cyclic mixed anhydride – bearing an exo-cyclic amino group – undergoes an intramolecular 1,4-acyl transfer rendering the canonical cyclopeptide **68** without noticeable epimerization. The reaction optimization was conducted for the synthesis of cyclic peptide **68a**, proving the high efficiency of the macrocyclization in the presence of 1.2 equiv of Ag_2CO_3, as evidenced by the clean conversion into the macrocycle. A variety of bioactive cyclic peptides were produced in good overall yields starting from the 2-chlorotrityl resin, with a single purification step after full side chain deprotection. The celogentin analog **68b**, the antibacterial gramicidin S (**68c**) and the RGD cyclopeptide **68d** stand among the most pharmacologically relevant macrocycles produced. Although this method cannot be referred to as catalytic due to need to employ stoichiometric amount of the metal salt, it features high efficiency, good kinetics and operational simplicity, while it is capable to bypass some common drawbacks of head-to-tail macrolactamization such as C-terminal epimerization and cyclodimerization.[138]

6. Conclusions and future perspectives

Over the last two decades, transition metal catalysis has experienced a notable expansion in the field of peptide late-stage derivatization and macrocyclization. The diversification of metal-catalyzed peptide cyclization technologies can be considered as one of the major advances in modern biomolecular chemistry. The reason for this lies at their ability to expand the peptide macrocycle chemotype space at a site where other methods fail to generate diversity, that is, the ring-forming moiety. Because of the early impact of palladium catalysis on peptide cyclization, the advent of novel palladium-catalyzed cross-coupling reactions has been received with enthusiasm by the peptide community. Thus, it is worth recognizing the positive impact that C–H activation has had on the diversification of metal-catalyzed derivatization processes, including macrocyclizations. The new trends are favoring late-stage peptide cyclizations with a minimum degree of pre-functionalization of the amino acid residues. In this sense, exploiting the activation potential of the native peptide backbone or the use of temporary, ideally traceless, directing groups is becoming highly efficient, and therefore more attractive for chemoselective macrocyclic ring closures. However, despite oxidative cross-coupling versions of the Heck macrocyclization have emerged (*i.e.*, C(sp^2)–H activation-based olefination), oxidative variants of alkyl–aryl, aryl–aryl (Suzuki–Miyaura type) and alkyne–aryl (Sonogashira type) cross-couplings are still elusive in the peptide macrocyclization realm. These latter would require the controlled intramolecular reaction of two specific hydrocarbon moieties among a forest of similar groups within the peptide structure. For this, fine-tuning the acidity, nucleophilicity, and directing group performance should be further improved. As such methods have been described for intermolecular reactions with rather simple substrates, it is expected that their macrocyclization variants will emerge in the near future.

Other classes of transformations with growing potential as peptide macrocyclization protocols are the metal-catalyzed annulation and heterocycle-ring formation. Besides the Larock indole annulation here described, a variety of rhodium[139,140] and ruthenium[141]-catalyzed macrocyclo-annulation and heterocyclization approaches have been recently reported with non-peptidic substrates. Such processes may be adapted to peptide stapling and main chain cyclization to generate eventually fused heterocyclic rings grafted into peptide macrocycles of medicinal chemistry interest.

Copper catalysis has also shown to be crucial for the rapid access to pharmacologically relevant cyclic peptides. Whereas macrocyclization approaches based on 'click' chemistry have evolved mostly in their cyclization tactic, new copper-catalyzed multicomponent reactions and cross-couplings have also been fine-tuned to achieve truly novel macrocyclization approaches. For example, a recent report by Romesberg, Baran and co-workers described a scalable synthesis of arylomycin cyclic peptides based on a copper-mediated oxidative phenol coupling that further expands the scope of C–H macrocyclizations.[142] Additionally, in the field of ring closing approaches involving terminal alkynes, there is still room for further diversification of both the metal and the reactivity modes. In this sense, interesting gold[143] and dual rhodium/Lewis acid[144]-catalyzed macrocyclizations of aliphatic alkynyl substrates have been recently disclosed, which seem to be well suited to implement with alkynyl peptides.

Finally, it is intriguing that only a few photoredox catalytic macrocyclizations have been described with peptides. Key to the diversification of such photochemical technologies in peptide cyclization chemistry is to broaden the combinations of dual transition metal/photoredox catalysis targeting specific functional groups. New organic photocatalysts, ligand modification and novel activation modes – based on fine-tuned interactions between the transition metal and the photoredox partner – shall expand the scope of photocatalysis in peptide derivatization. Besides the decisive chemoselectivity, the field should move to seek regio- and stereoselective macrocyclizations, which are crucial in peptide drug development. Overall, we consider that many exciting applications will emerge by applying metal catalysis to fix the conformation of rationally designed bioactive peptide sequences. Opportunities for creating new macrocyclic topologies are just waiting for synthetic chemists interested on leveraging the expertise in metal catalysis to cyclize peptides.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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