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Review

Transition-Metal-Catalyzed C–C Bond Macrocyclization via Intramolecular C–H Bond Activation

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Abstract: Macrocycles are commonly synthesized via late-stage macrolactamization and macrolactonization. Strategies involving C–C bond macrocyclization have been reported, and examples include the transition-metal-catalyzed ring-closing metathesis and coupling reactions. In this mini-review, we summarize the recent progress in the direct synthesis of polyketide and polypeptide macrocycles using a transition-metal-catalyzed C–H bond activation strategy. In the first part, rhodium-catalyzed alkene–alkene ring-closing coupling for polyketide synthesis is described. The second part summarizes the synthesis of polypeptide macrocycles. The activation of indolyl and aryl C(sp^2)–H bonds followed by coupling with various coupling partners such as aryl halides, arylates, and alkynyl bromide is then documented. Moreover, transition-metal-catalyzed C–C bond macrocyclization reactions via alkyl C(sp^3)–H bond activation are also included. We hope that this mini-review will inspire more researchers to explore new and broadly applicable strategies for C–C bond macrocyclization via intramolecular C–H activation.

Keywords: transition-metal catalysis; C–H activation; macrocyclization; polyketide macrocycles; polypeptide macrocycles

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Citation: Wang, X.; Lu, M.-Z.; Loh, T.-P. Transition-Metal-Catalyzed C–C Bond Macrocyclization via Intramolecular C–H Bond Activation. *Catalysts* **2023**, *13*, 438. https://doi.org/10.3390/catal13020438

Academic Editors: Ewa Kowalska and Yuichi Kobayashi

Received: 17 January 2023
Revised: 14 February 2023
Accepted: 15 February 2023
Published: 17 February 2023

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1. Introduction

Macrocycles have been defined as cyclic molecules that contain 12 or more covalent connected atoms, which are featured widely in numerous biologically active natural products and pharmaceutically relevant molecules (Figure 1) [1,2]. Among them, polypeptide and polyketide macrocycles are the most common. For the synthesis of this important class of compounds, one of the crucial steps is the late-stage macrocyclization reaction [3–10]. As these precursors leading to the molecules may have different conformational structures, the key step involving intramolecular the macrocyclization reaction can been challenging. The common strategies reported so far include macrolactonization [11–13], macrolactamization [14–16], and macroaldolization [17–19] (Figure 2). Over the decades, transition-metal-catalyzed intramolecular coupling and ring-closing metathesis (RCM) have also been shown to be effective strategies for constructing large rings [20–23]. However, all of the reported methods have some disadvantages, such as the need to use expensive catalysts, difficulty in accessing the substrates, and difficulty in introducing alkene functionality with high selectivity. Furthermore, many of these methods are not atom-economical and sometimes produce substantial amounts of hazardous wastes that are difficult to treat.

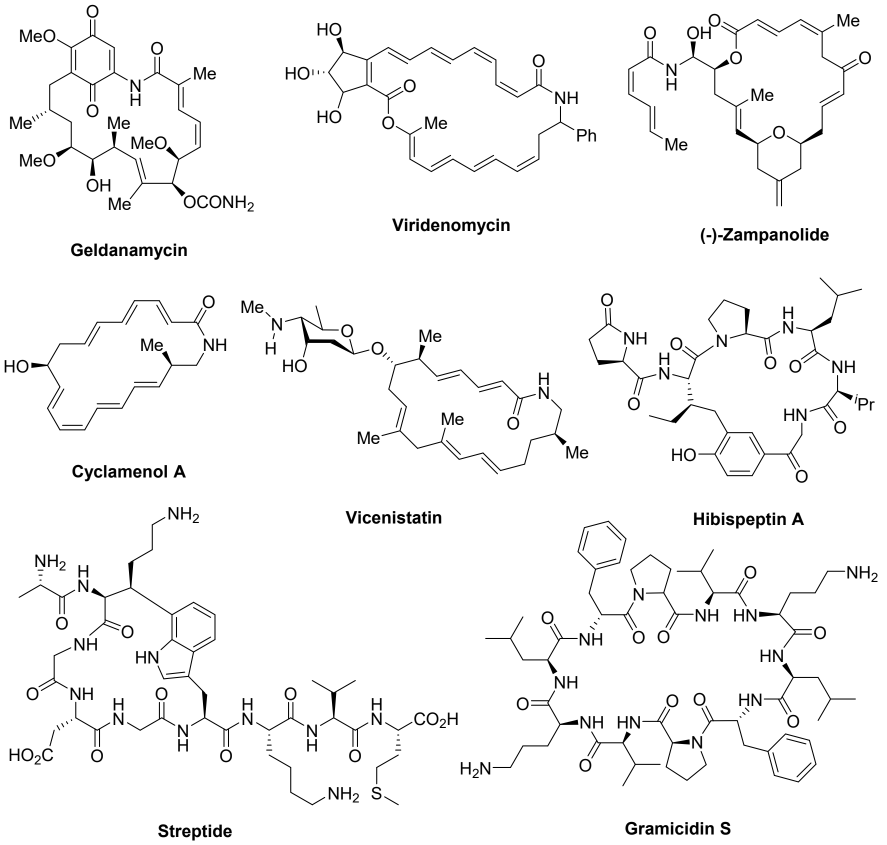


Figure 1. Representative examples of bioactive macrocyclic natural products.

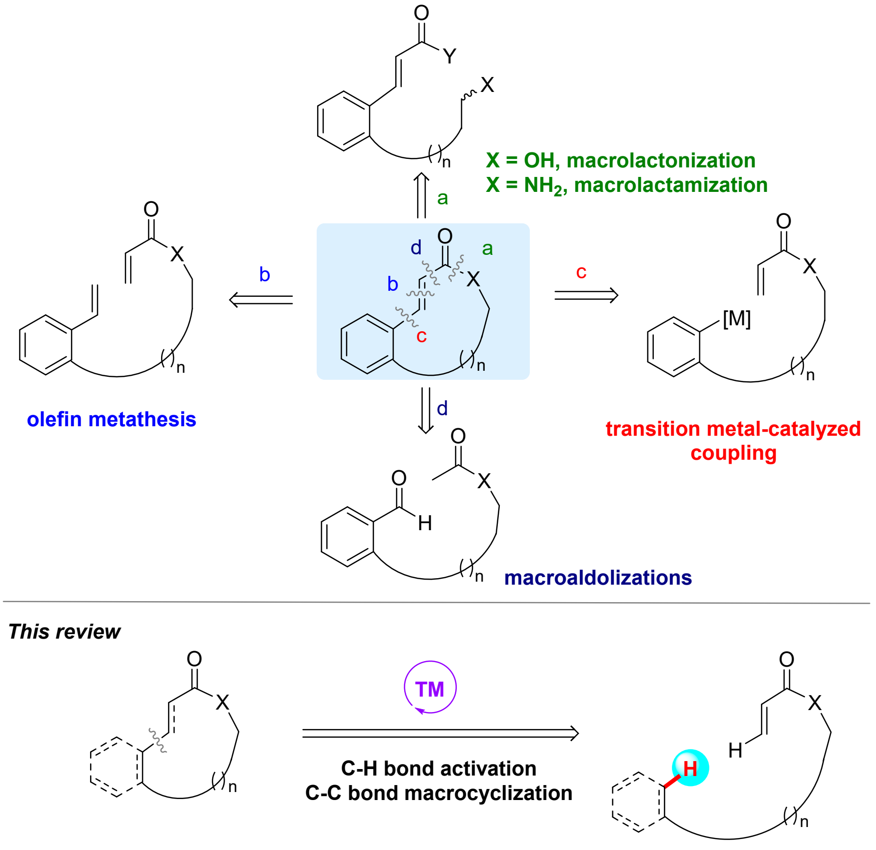


Figure 2. General strategies for the direct synthesis of macrocycles.

In recent years, transition-metal-catalyzed C–H activation reactions have attracted increasing attention [24–31]. In contrast to the classical cross-coupling reactions, such as Suzuki coupling, Negishi coupling, and Stille coupling, the C–H bond functionalization coupling reactions do not need to use organometallic or organohalide reagents. Due to these remarkable advantages, the C–H bond functionalization reactions have been utilized widely in organic synthesis, and a large number of excellent reviews on this topic have also been reported [32–43]. While the intermolecular versions of metal-catalyzed, group-controlled C(sp^2)–H for aryl groups and vinyl groups and C(sp^3)–H for alkyl groups have been well studied, the application of the intramolecular version of macrocyclization to construct various macrocycles has remained relatively unexplored [44–47]. The lengthy synthesis of the precursors for the risky macrocyclization step may be one of the main reasons. In recent years, we have witnessed more activities in the polypeptide area as compared to polyketide synthesis. In this mini-review, we will mainly focus on the direct synthesis of polyketide and polypeptide macrocycles involving carbon–carbon-based cyclization reactions via intramolecular C–H bond macrocyclization reactions (Figure 2) [48].

2. Polyketide Macrocycles

Macrolides containing a diene moiety are found in many bioactive natural products such as vicenistatin [49–51], geldanamycin [52,53], and cyclamenol A [54]. Therefore, the development of robust methods to construct structurally diverse macrocycles via C–C bond macrocyclization containing a fixed configuration of the diene moiety can be challenging. Extending the reactions they developed for the intermolecular version [55], Loh's group in 2018 first reported an efficient method to construct macrolactams containing diene functionality with high *Z* and *E* selectivity via an alkenyl sp^2 C–H bond olefination using a Cp*Rh(III) catalyst (Figure 3) [56]. This strategy provides easy access to a wide variety of macrocodes with different ring sizes in an atom-economical manner. Mechanistically, this ring-closing alkene–alkene coupling reaction was proposed to proceed via a *Z*-olefinic vinylrohodium(III) intermediate of the acrylamide derivative (Figure 4). Initially, the anion exchange of the $[RhCp^*Cl_2]_2$ catalyst with the NaBARF additive and $Cu(OAc)_2{\bullet}H_2O$ produced the highly reactive species **A**, which then selectively activated the *Z*-olefinic C(sp^2)–H bond of acrylamides to generate the vinylrhodium(III) intermediate **B**. Subsequent coordination and further migratory insertion occurred smoothly to afford the intermediate **D**, which finally underwent facile β-H elimination to give the macrocycle product.

The intramolecular alkene–alkene ring cyclization reaction using the rhodium catalyst led to various macrocycles containing a versatile dienoate moiety. The conjugated moiety present in the resulting macrocycles is highly versatile and can be converted into many different functional groups, thereby allowing easy access to macrolides containing different functionalities (Figure 5). For example, the hydrogenation of the macrocyclization product in the presence of the Pd/C catalyst afforded the saturated alkane product. The treatment of the product with a copper catalyst with $PhMe_2Si$-BPin furnished the 1,4-hydrosilylation product. On the other hand, reacting the product with the bis(pinacolato)diboron reagent led to the formation of the internal alkene product. Subjecting the product to nitromethane in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) led to the 1,4-Michael addition product. Overall, the versatility of the dienoate products allowed easy access to a wide variety of useful macrocycles that were not easily accessible using the reported methods.

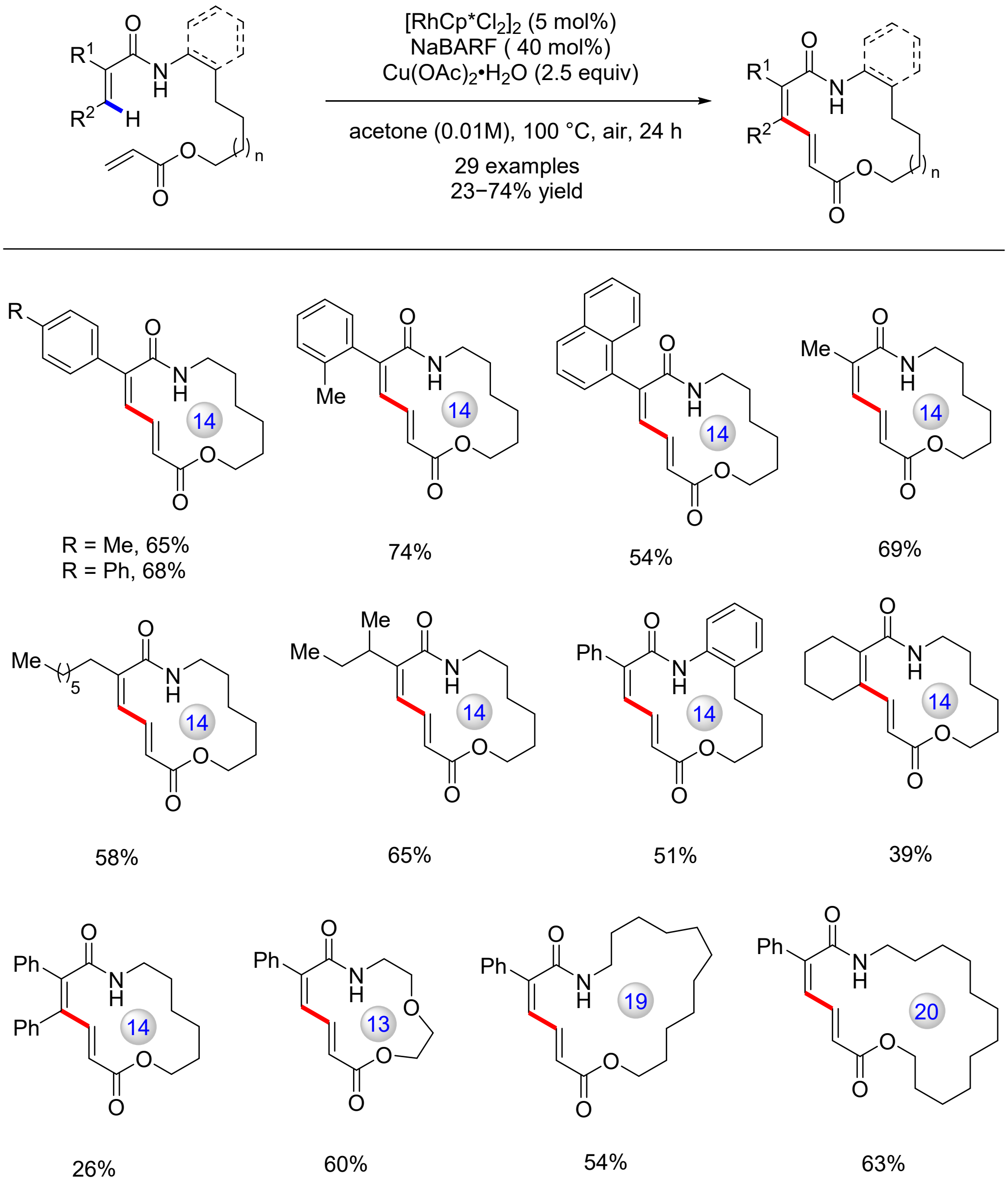


Figure 3. Macrolide synthesis via Cp*Rh(III)-catalyzed intramolecular oxidative cross-coupling of alkenes [56].

In 2020, the Loh group further expanded their intramolecular ring-closing alkene–alkene coupling strategy to α,β-unsaturated ketone substrates (Figure 6) [57]. Under the same conditions, a wide variety of macrolactams of different ring sizes were synthesized in moderate to good yields (33−72%). Of note, the intramolecular coupling of the alkene substrate with no substitution at the α-position also proceeded smoothly to furnish the corresponding macrolactam at a 44% yield. Moreover, this protocol could afford more strained 12- and 13-membered ring macrolactams in satisfactory yields. The authors proposed an analogous catalytic mechanism to elucidate this Cp*Rh(III)-catalyzed alkenyl C(sp^2)–H activation–macrocyclization pathway.

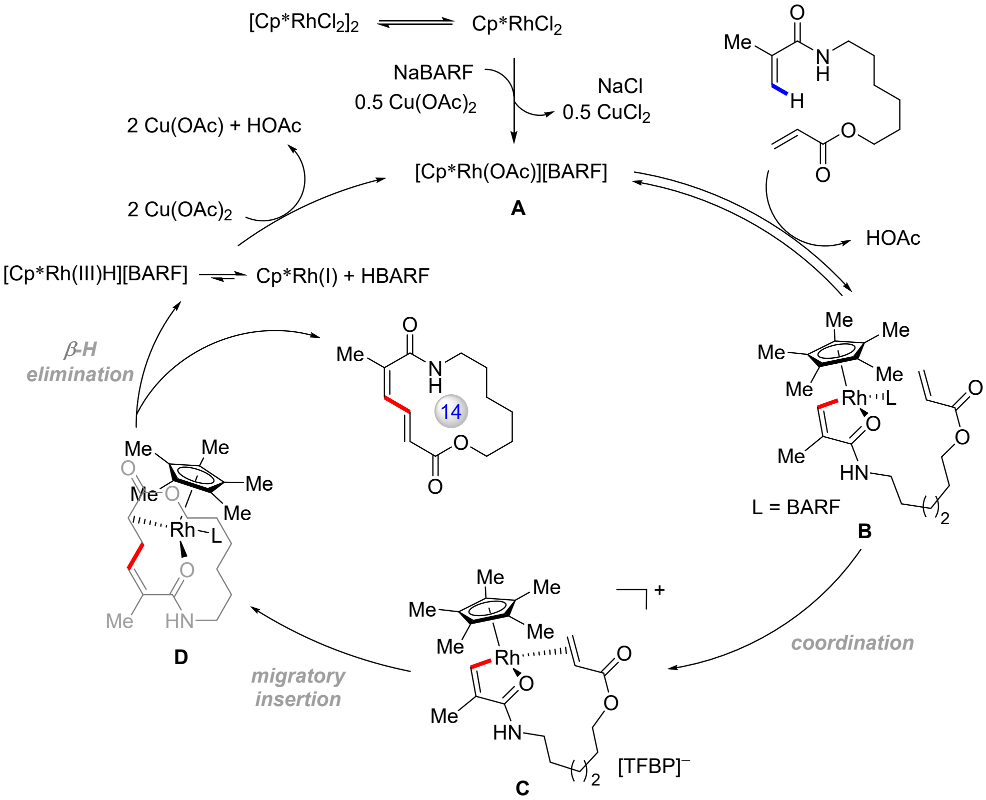


Figure 4. Proposed mechanism for the Cp*Rh(III)-catalyzed intramolecular alkenyl sp^2 C–H activation–macrocyclization [56].

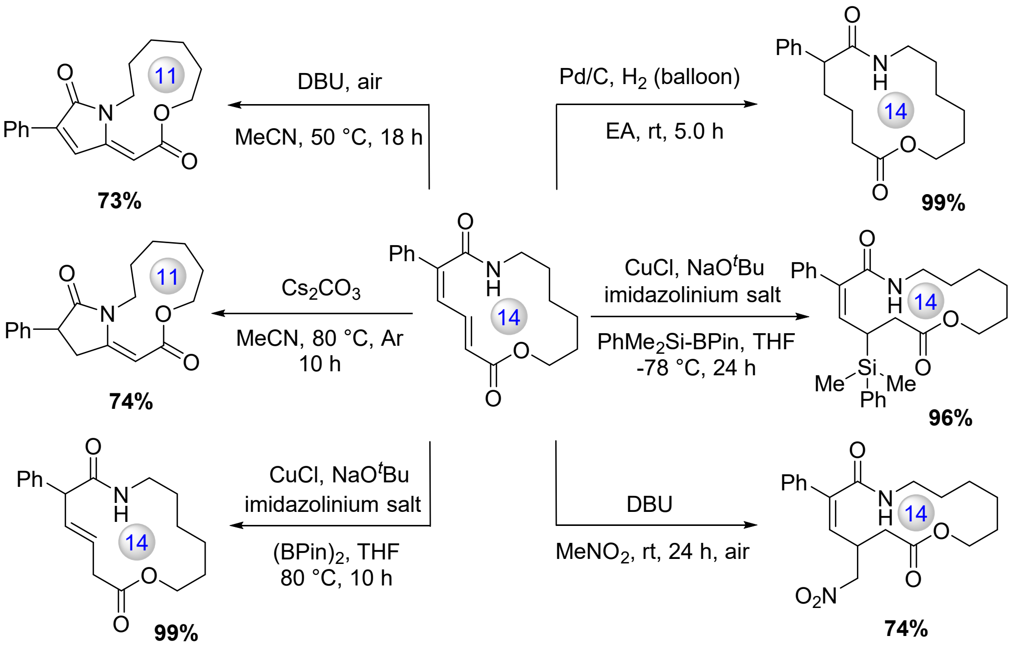


Figure 5. Synthetic derivatization of the cross-coupling macrocycle product [56].

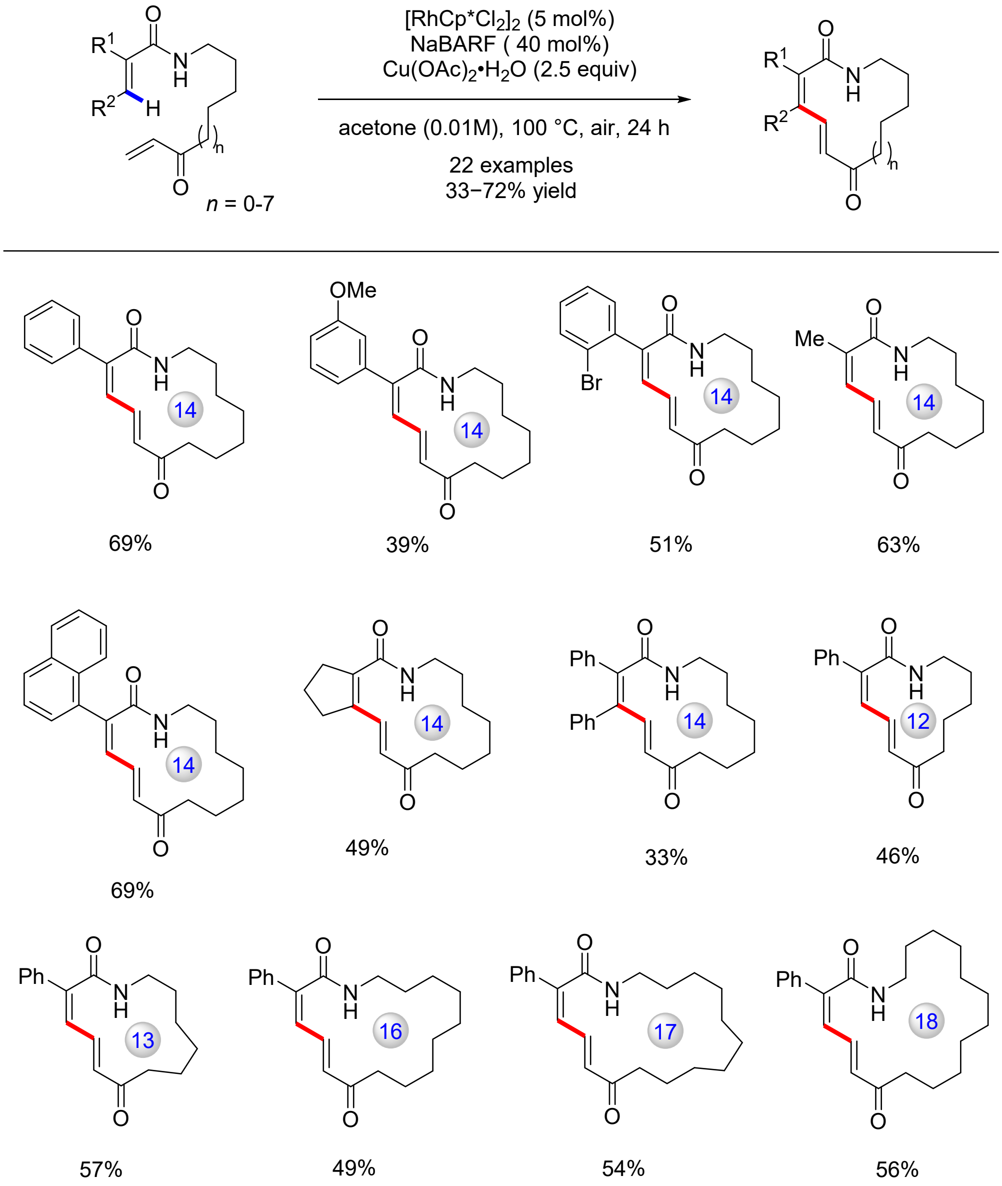


Figure 6. Macrolactam synthesis via Cp*Rh(III)-catalyzed intramolecular ring-closing alkene−alkene cross-couplings [57].

3. Polypeptide Macrocycles

Peptide-based macrocycles have been shown to have a wide variety of biological activities [58]. Some important drugs such as the antibiotic vancomycin [59], anti-cancer agent octreotide [60], and immunosuppressant cyclosporine [61] contain a peptide macrocycle structure. Furthermore, in contrast to linear peptides, peptide macrocycles have improved properties in terms of cell penetration, stability, and selectivity. In recent years, cyclic peptides have also been used as the delivery systems in peptide–drug conjugates such as ^{177}Lu-dotatate [62] and edotreotide gallium Ga-68 [63]. In addition to the amide bond formation strategy, the use of C–H bond functionalization strategies has gained tremendous attention in recent years due to their ability to construct many different stapled cyclopeptides. In this part of the review, we will divide them into 3 different categories: (1) in the first part, we will focus mainly on the sp^2 C–H bond functionalization of indole C–H bond macrocyclization; (2) in the second part, we will focus mainly on the C–H bond functionalization of the aryl C(sp^2)–H bond macrocyclization strategy; (3) in the final part, we will discuss the recent progress in the inert C(sp^3)–H bond (both with and without a directing group) functionalization macrocyclization strategy.

3.1. C(sp^2)–H Bond Functionalization of Indoles

The macrocyclization reactions involving C(sp^2)–H bond activation can be grouped into 2 categories. The first group involves the sp^2 C–H bond activation of the indole of Trp residues to couple with different coupling partners. With the assistance of microwave irradiation, James and co-workers in 2012 first developed a general palladium-catalyzed method to activate indole C–H bonds of tryptophan derivatives bearing aromatic iodide side chains for peptide macrocyclization through a Pd(0)/Pd(II) redox manifold, enabling the formation of diverse indole–aryl-bridged macrocycles (Figure 7) [64]. In the presence of 2-NO$_2$-BzOH and AgBF$_4$ additives, the macrocyclization reaction was typically finished within 30 min at 130 °C in dimethylacetamide (DMA), which could occur at a remarkably moderate concentration (30 mM). Both *para*- and *meta*-substituted aromatic iodides could be tolerated with the current protocol, generating a variety of 15- to 25-membered rings macrocyclization products in yields ranging from 40% to 75%. Of note, unprotected Tyr was also tolerated in this strategy.

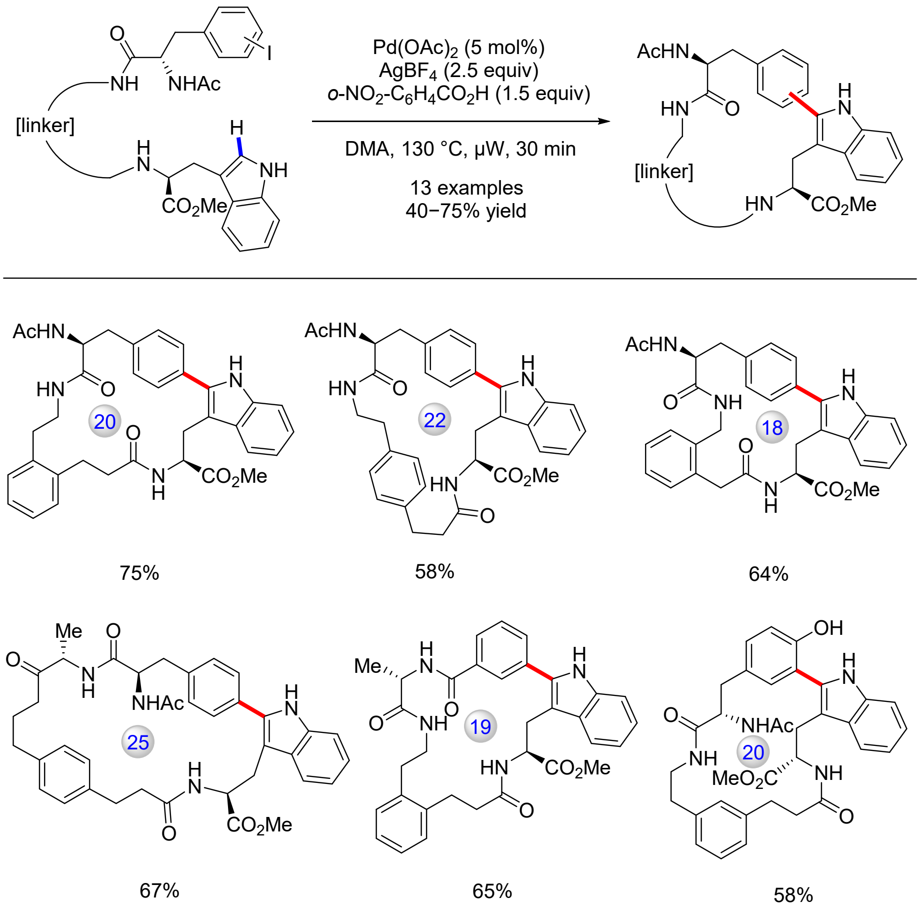
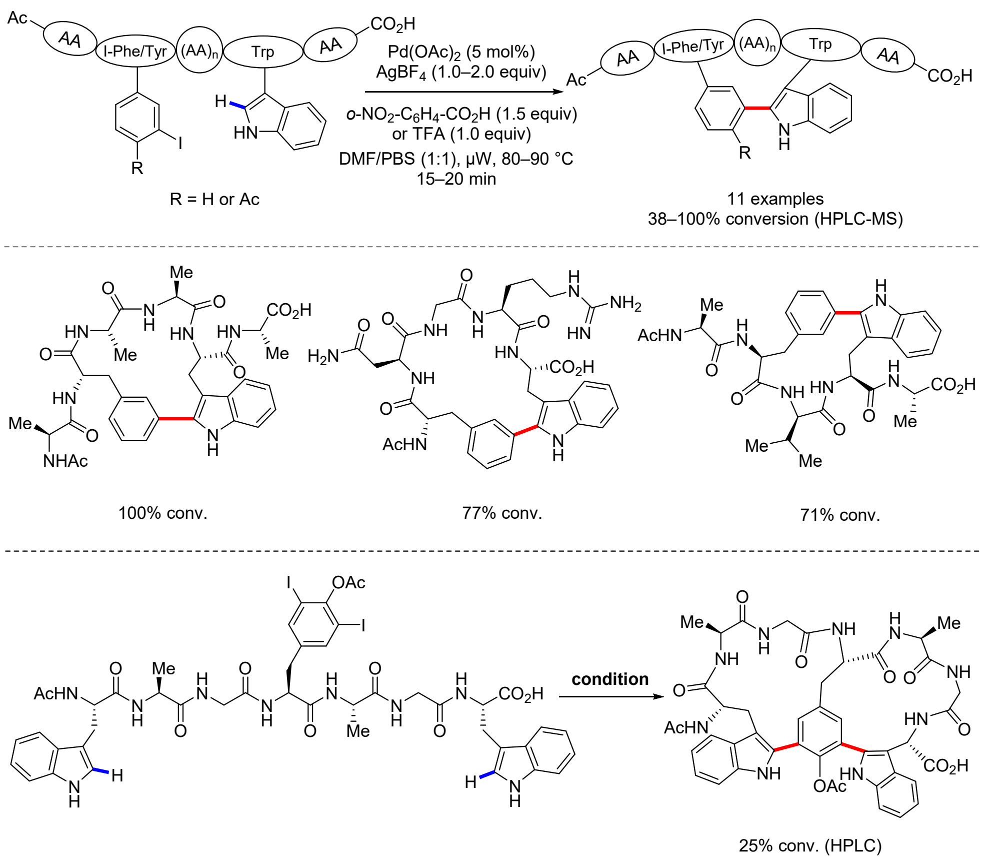


Figure 7. Synthesis of cyclic peptides via palladium-catalyzed intramolecular indole C-2 C–H bond arylation [64].

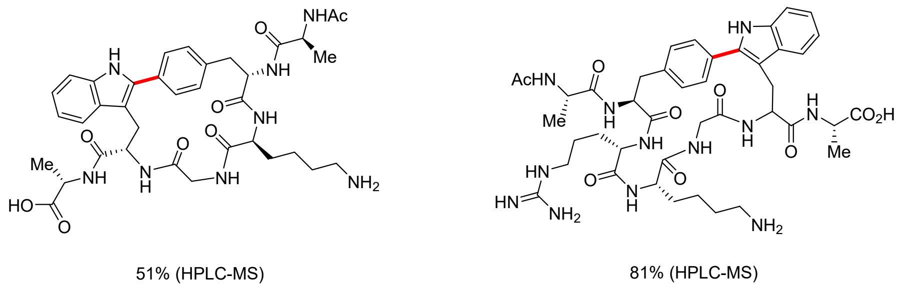
Later, in 2015, Albericio, Lavilla, and their co-workers extended their Pd-catalyzed C–H activation–macrocyclization protocol, and further demonstrated the intramolecular C–H bond arylation of indoles of Trp residues at the C2 position with different aryl halides to construct structurally more complex and constrained cyclopeptides containing unique Trp(C4)–arene cross-links (Figure 8a) [65] This transformation was compatible with a series of unprotected amino acid units such as Arg, Gln, Asp, and Ser, which could be applied to both solution-phase and solid-phase peptide synthesis processes. Using this strategy, the authors were able to synthesize a double stapled bicyclic peptide in a 25% HPLC conversion process, which proved extremely difficult to prepare using previously reported methods. It should be noted that the competing intermolecular cyclodimerization associated with this strategy selectively generated cyclodimeric peptides. In order to obtain the determining factors in controlling the fate of the transformation, Lavilla et al. further carried out a systematic study of the intermolecular C–H bond arylation of Trp residues bearing iodinated aromatic side chains, and the results showed that linear peptides containing a *meta*- or *para*-iodophenylalanine unit at adjacent positions selectively afforded cyclic dimers instead of stapled peptides. Increasing the chain length of the residues remarkably resulted in the generation of peptide-based macrocycles (Figure 8b) [66].

(a) **Albericio**, **Lavilla** et al., **2015**



Condition: $Pd(OAc)_2$ (40 mol%), $AgBF_4$ (6.0 equiv), PivOH (1.5 equiv), DMF, μW, 90 °C, 20 min

(b) **Lavilla** et al., **2016**



Condition: $Pd(OAc)_2$ (20 mol%), $AgBF_4$ (2.0 equiv), TFA (1.0 equiv), DMF (0.10–0.25 M), μW, 90 °C, 20 min

Figure 8. Synthesis of stapled peptides via palladium-catalyzed intramolecular $C(sp^2)$–H bond arylation [65,66].

In 2020, Liu and co-workers reported the activation of the C(sp^2)–H bond of the *N*-protected indole at the C2 position with the assistance of the 2-pyridyl directing group enabled by Cp*Rh(III) catalysis. Under the typical reaction conditions of $[RhCp^*Cl_2]_2$ (10 mol%), Ag_2O (20 mol%), and AgOAc (1.5 equivalent) in CH_3CN at 80 °C, the intramolecular C(sp^2)–H bond coupling with a tethered maleimide moiety proceeded uneventfully to provide 3 examples of maleimide-decorated, tryptophan-based macrocyclic peptides in moderate yields (Figure 9) [67].

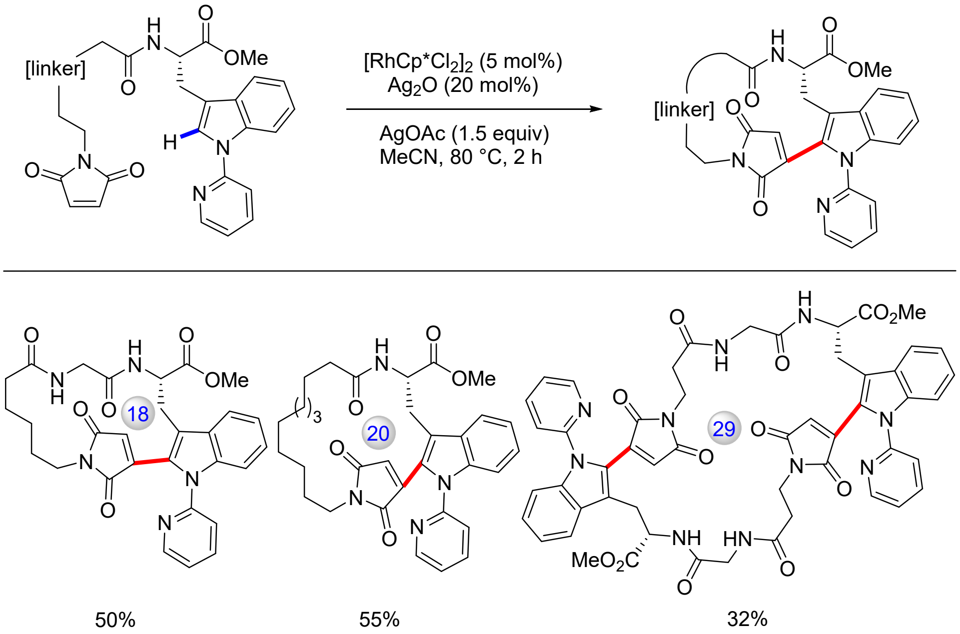
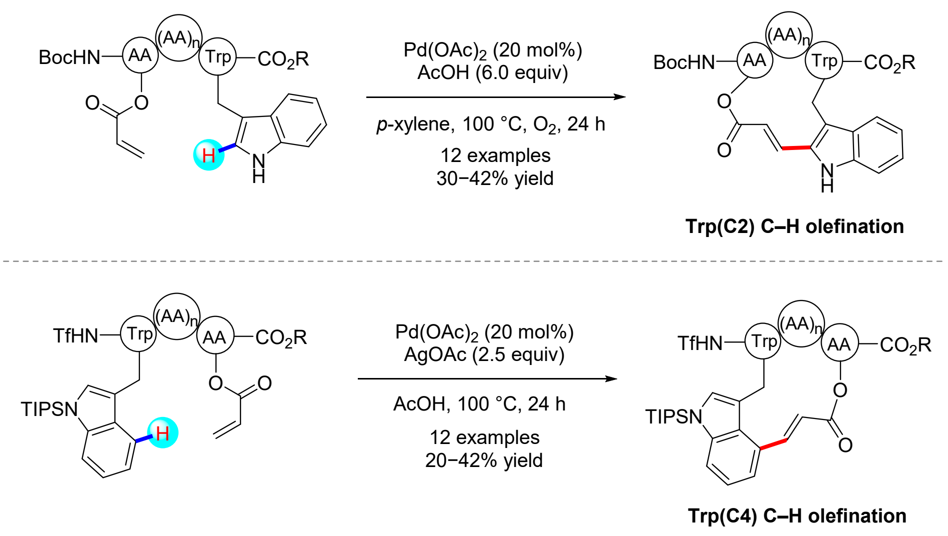


Figure 9. Synthesis of maleimide-decorated peptide macrocycles via the Cp*Rh(III)-catalyzed intramolecular C(sp^2)–H alkenylation of tryptophan [67].

In an effort to achieve highly regioselective late-stage peptide macrocyclization, Wang et al. in 2020 utilized the peptide backbone as endogenous directing groups to promote site-selective peptide macrocyclization at Trp(C2) (Figure 10a) [68]. Using the combination of a $Pd(OAc)_2$ (10 mol%) catalyst and AcOH (6.0 equivalent) additive under an O_2 (1.0 atm) atmosphere in *para*-xylene at 100 °C, 12 examples of peptide-based macrocycles with unique Trp–alkene cross-links were documented in reasonable yields (20–42%). Under modified conditions, the authors were able to synthesize macrocyclic peptides containing unique Trp(C4)–alkene cross-links enabled by the palladium-catalyzed C(sp^2)–H olefination at the C4 position of Trp residues bearing a TfNH-directing group (Figure 9a) [65]. More recently, the same group further extended this method to realize the rhodium(I)-catalyzed regioselective intramolecular C(sp^2)–H bond alkylation of Trp residues bearing a *N*-P^{t}Bu$_2$ directing group, providing efficient access to diverse peptide macrocycles with Trp(C7)-alkyl cross-links (Figure 10b) [69].

In 2017, The Ackerman group successfully utilized alkynyl bromide as an internal coupling partner for the cost-effective manganese(I)-catalyzed late-stage macrocyclization of 2-pym-protected indole of indole Trp residue, giving rise to a 21-membered, peptide-based macrocycle with aryl-alkyne cross-links at a 53% yield (Figure 11) [70].

(a) **Wang** et al., **2020**



(b) **Shi**, **Wang** et al., **2022**

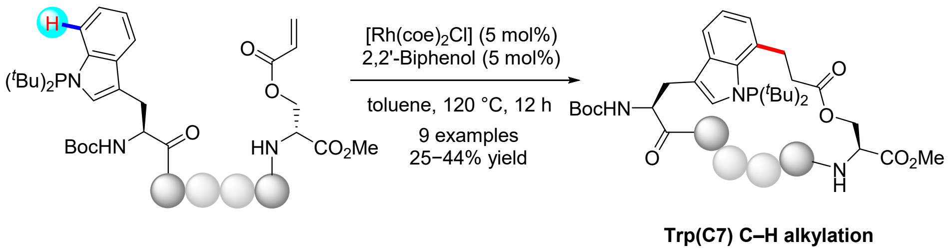


Figure 10. Peptide macrocyclizations via site-selective intramolecular C(sp^2)–H bond functionalization of tryptophan [68,69].

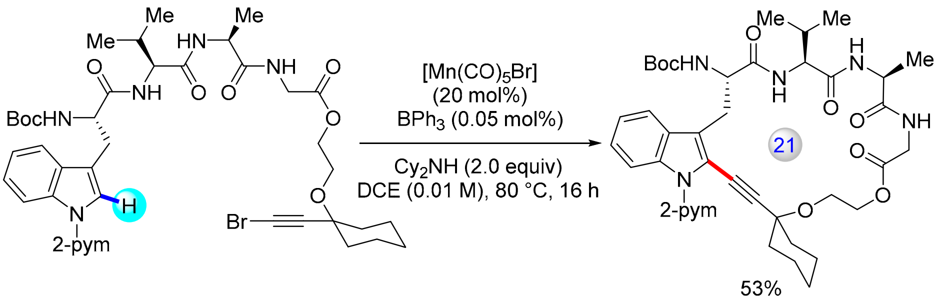


Figure 11. Peptide macrocyclization via manganese-catalyzed intramolecular C(sp^2)–H alkynylation [70].

3.2. *C(sp^2)–H Bond Functionalization of Arenes*

Besides the above-mentioned examples of C(sp^2)–H bond functionalization of indole of tryptophan, the intramolecular macrocyclization reactions via transition-metal-catalyzed C(sp^2)–H bond functionalization of simple arenes have also been investigated in recent years. In 2019, Wang and colleagues elaborated a general backbone-directed approach to fabricate macrocycle peptides with biaryl cross-links via the palladium-catalyzed intramolecular *ortho*-C(sp^2)–H arylation of short peptides with tethered aromatic iodide side chains (Figure 12) [71]. The *N*-terminal benzamides of the peptide backbone act as efficient directing groups in this strategy, which significantly facilitate this site-specific arylation process. Under the reaction conditions, biaryl-bridged cyclic peptides with different ring sizes were synthesized in reasonable yields (20–40%). Moreover, this protocol was also applicable to the intermolecular *ortho*-C(sp^2)–H arylation of various oligopeptides, furnishing a series of biaryl-linked products in good yields.

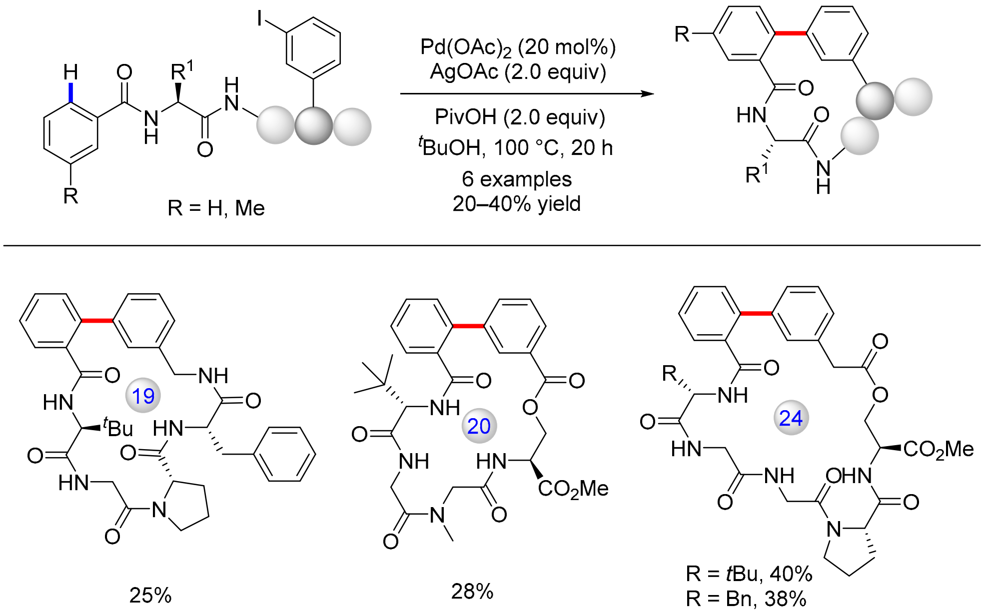


Figure 12. Macrocyclization of biaryl-bridged cyclic peptides via palladium-catalyzed intramolecular C(sp^2)–H bond activation [71].

In a subsequent study, Chen and co-workers disclosed a versatile approach for the synthesis of diverse cyclophane-braced macrocycle peptides through the efficient picolinamide-directed intramolecular aromatic γ- and δ-C(sp^2)–H arylation of readily accessible linear peptide precursors with aryl iodides (Figure 13) [72]. The judicious choice of silver additive was found to be critical for high efficiency. The intramolecular aromatic C(sp^2)–H arylation reactions occurred smoothly in the presence of the $Pd(CH_3CN)_4(BF_4)_2$ (10 mol%) catalyst and 1.5 equivalent of AgOBz additive at 130 °C. Under modified conditions of $Pd(OAc)_2$ and AgOAc in hexafluoroisopropanol (HFIP), the alkenyl counterparts were also compatible with the C–H sources for this approach, giving rise to the corresponding aryl–vinyl C(sp^2)-linked peptide-based macrocycles in moderate yields. However, a remarkable 1:1 mixture of γ- and δ-arylated products was observed for the alkenyl C(sp^2)–H arylation of a smaller ring size. Mechanistically, the reaction was suggested to occur via Pd(II)-catalyzed C(sp^2)–H activation to produce a putative palladacycle species. The subsequent oxidative addition (OA) with tethered aryl iodides generated the key Pd(IV) intermediate, which finally underwent reductive elimination (RE) to afford the C–H activation–macrocyclization product.

The Wang group in 2018 reported the straightforward synthesis of macrocycle peptides with unique aryl–vinyl cross-links via the late-stage palladium-catalyzed δ-C(sp^2)–H olefination of phenylalanine (Phe) residues (Figure 14) [73]. The peptide backbone amides were readily employed as internal directing groups to facilitate the macrocyclization of peptides in the N-to-C direction. This macrocyclization protocol tolerated a broad range of short peptides, generating a variety of peptide-based macrocycles of different sizes and shapes. Both activated and unbaised aliphatic alkenes were viable coupling partners for this macrocyclization. Moreover, the authors also demonstrated the utility of this protocol via the synthesis of a structurally constrained bicyclic peptide via the one-pot macrocyclization of β-C(sp^2)–H arylation and δ-C(sp^2)–H olefination reactions.

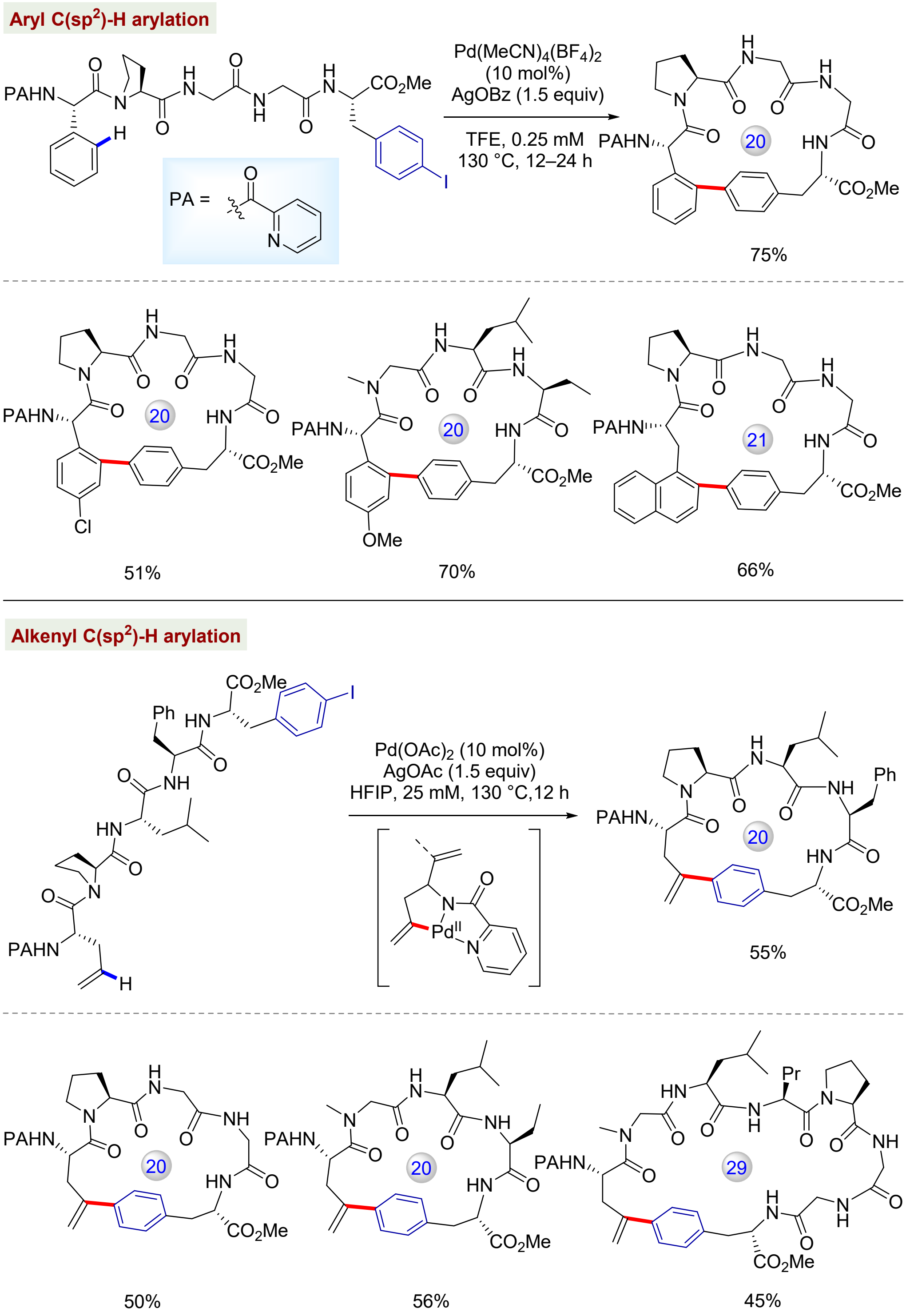


Figure 13. Synthesis of cyclophane-braced peptide macrocycles through palladium-catalyzed intramolecular vinyl and aryl C(sp^2)–H arylation [72].

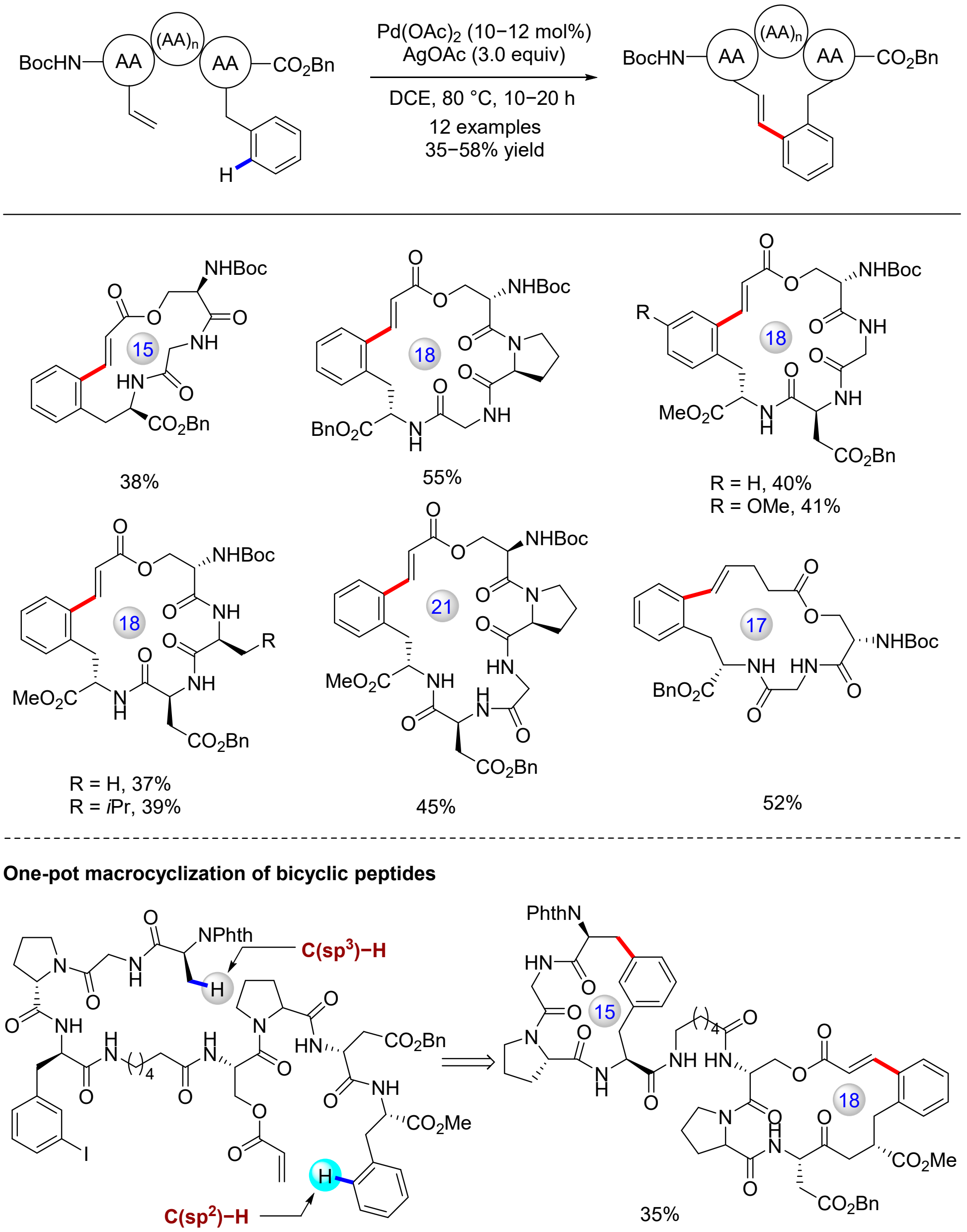


Figure 14. Peptide macrocyclization via Pd(II)-catalyzed intramolecular δ-C(sp^2)–H olefination of phenylalanines [73].

In the same year, Wang and co-workers also reported a peptide-guided C(sp^2)–H activation method for the late-stage macrocyclization of various sulfonamide-containing peptides via intramolecular *ortho*-directed C(sp^2)–H alkenylation, which was significantly facilitated by the internal peptide backbone (Figure 15) [74]. Using the *N*-sulfonated peptides as endogenous directing groups, this macrocyclization protocol featured a broad substrate scope and tolerated both activated acrylates and unbaised aliphatic alkenes, giving rise to a series of bioactive peptidosulfonamide macrocycles with aryl–alkene cross-links over a 34–72% yield range. As an extension of this approach, the same group in 2019 further achieved the macrocyclization reaction of peptidoarylacetamides under identical conditions (Figure 16) [75].

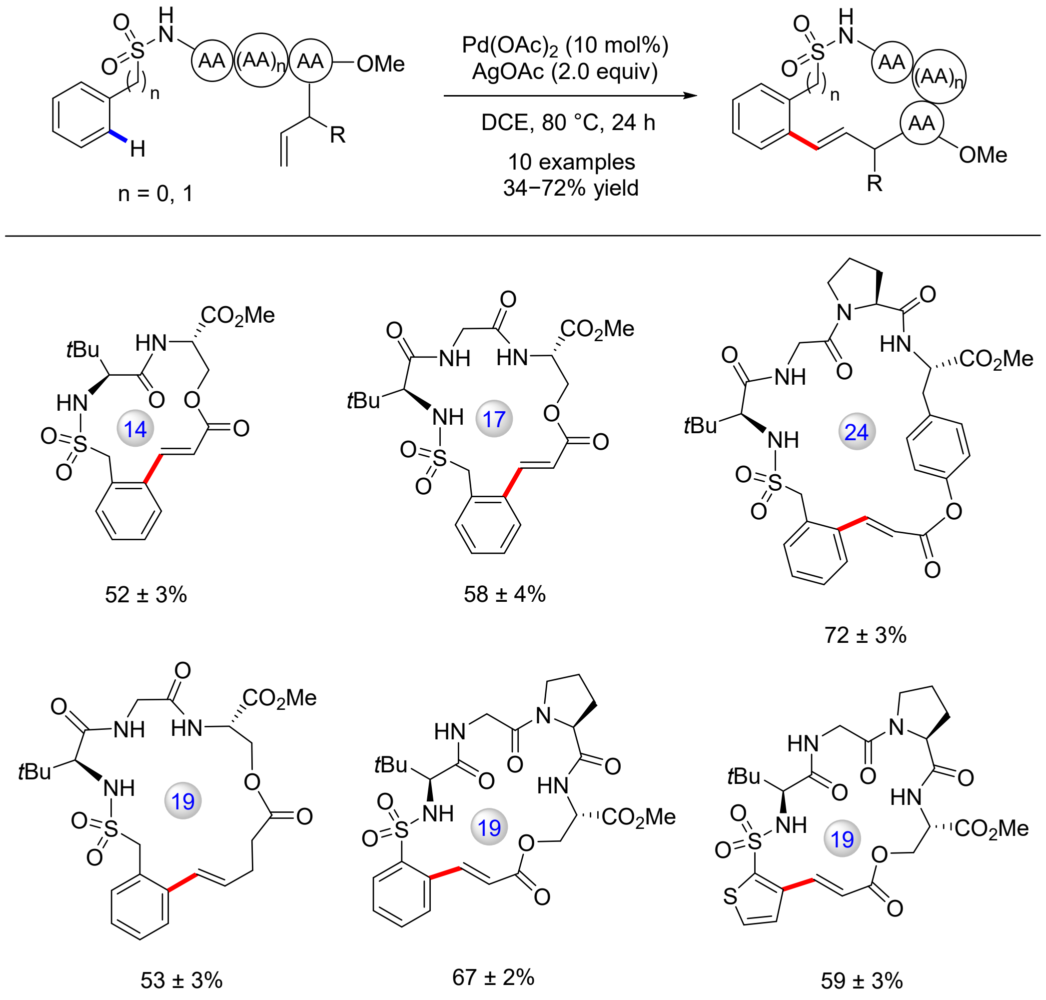


Figure 15. Macrocyclization of peptidosulfonamides via palladium(II)-catalyzed intramolecular C(sp^2)–H bond olefination [74].

Subsequently, Wang and colleagues continued their versatile macrocyclization strategy [76], and further accomplished an efficient late-stage macrocyclization reaction of various bioactive oxazole-containing peptides through the intramolecular palladium-catalyzed δ-C(sp^2)–H olefination (Figure 17a) [77]. In this report, the oxazole motifs in the peptide backbones acted as endogenous directing groups to promote this *ortho*-C(sp^2)–H olefination reactions. The resulting oxazole-containing cyclic peptides bearing aryl–alkene cross-links showed strong cytotoxicity toward cancer cells. Quite recently, Wang et al. further expanded to report on the late-stage modification and macrocyclization of diverse thiazole-containing peptides, generating a series of 21–25 membered bioactive peptide-based macrocycles in 35–59% yields (Figure 17b) [78].

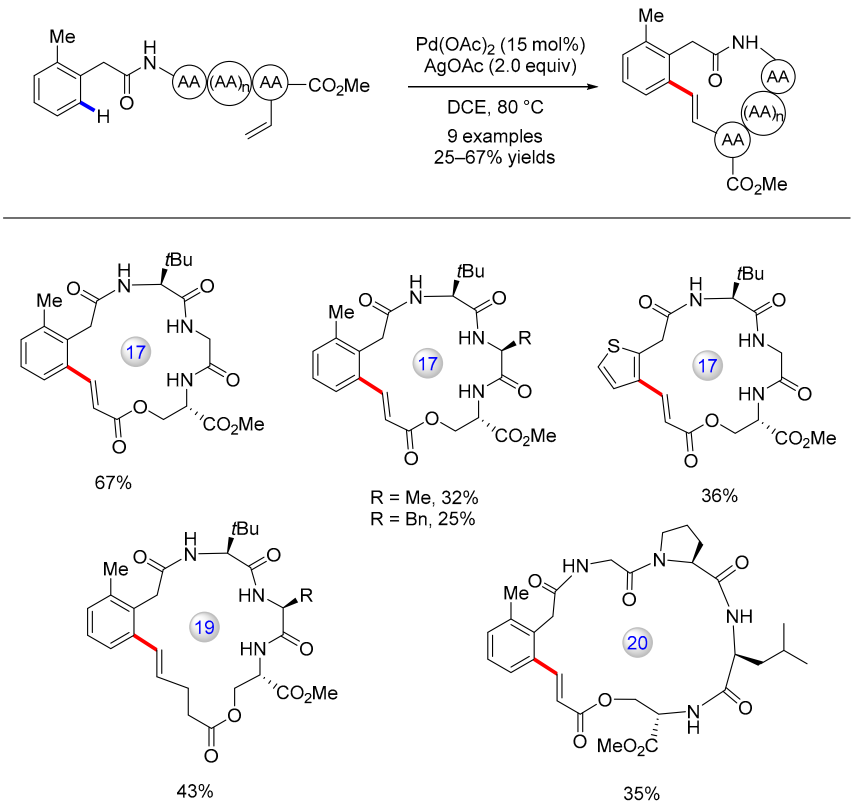
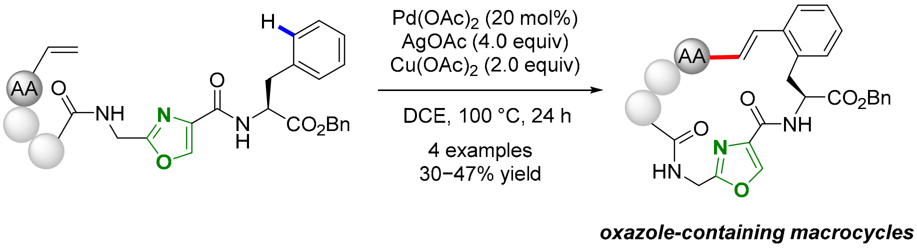


Figure 16. Macrocyclization via Pd(II)-catalyzed intramolecular C(sp^2)–H olefination of peptidoarylacetamides [75].

a) **Tan**, **Wang** et al., **2021**



b) **Bai**, **Wang** et al., **2022**

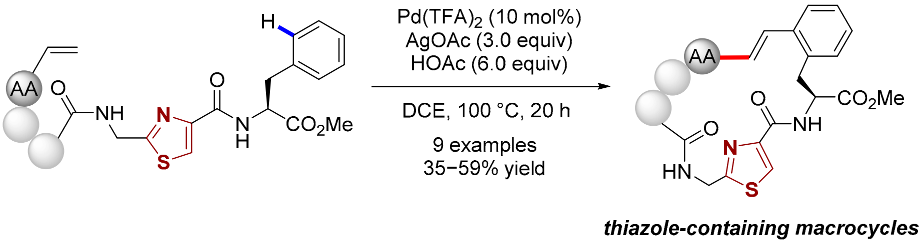


Figure 17. Late-stage macrocyclization via intramolecular δ-C(sp^2)–H bond olefination of oxazole-and thiazole-containing peptides [77,78].

3.3. C(sp^3)–H Bond Functionalization

In recent years, there has been much interest in the development of stapled peptides, including polypeptide macrocycles, for drug discovery. Simultaneously, the construction of C–C cross-linked stapled peptides using the C–H activation coupling strategies has also emerged as an attractive strategy for peptide-based macrocycles synthesis. Although there are many reports on the intermolecular C(sp^3)–H bond functionalization of amino acids and peptides [79–81], the intramolecular version of C(sp^3)–H bond functionalization for polypeptide macrocycles synthesis is still very rare. Inspired by Yu's backbone-assisted inert C(sp^3)–H activation strategy for the late-stage derivatization of various short peptides [82], Albericio, Noisier, and co-workers in 2017 elegantly established an efficient palladium-catalyzed C(sp^3)–H activation method without relying on any external directing group for peptide stapling (Figure 18) [83]. Unprecedentedly, this process allowed the linkage between *N*-terminal alanine (Ala) and *C*-terminal phenyl alanine (Phe) residues. The role of the solvent was found to be crucial for this peptide macrocyclization process, and using *t*-BuOH as the co-solvent they significantly suppressed the unwanted side reactions. Under the optimized reaction conditions, the intramolecular C(sp^3)–H arylation of *N*-terminal Ala with *meta*-iodinated Phe proceeded smoothly with good to excellent conversion rates, and a wide variety of cyclic hydrocarbon cross-linked polypeptides bearing different ring sizes macrocycles were synthesized in modest yields. Moreover, this strategy is also compatible with solid-phase peptide synthesis, enabling the rapid synthesis of new peptide motifs.

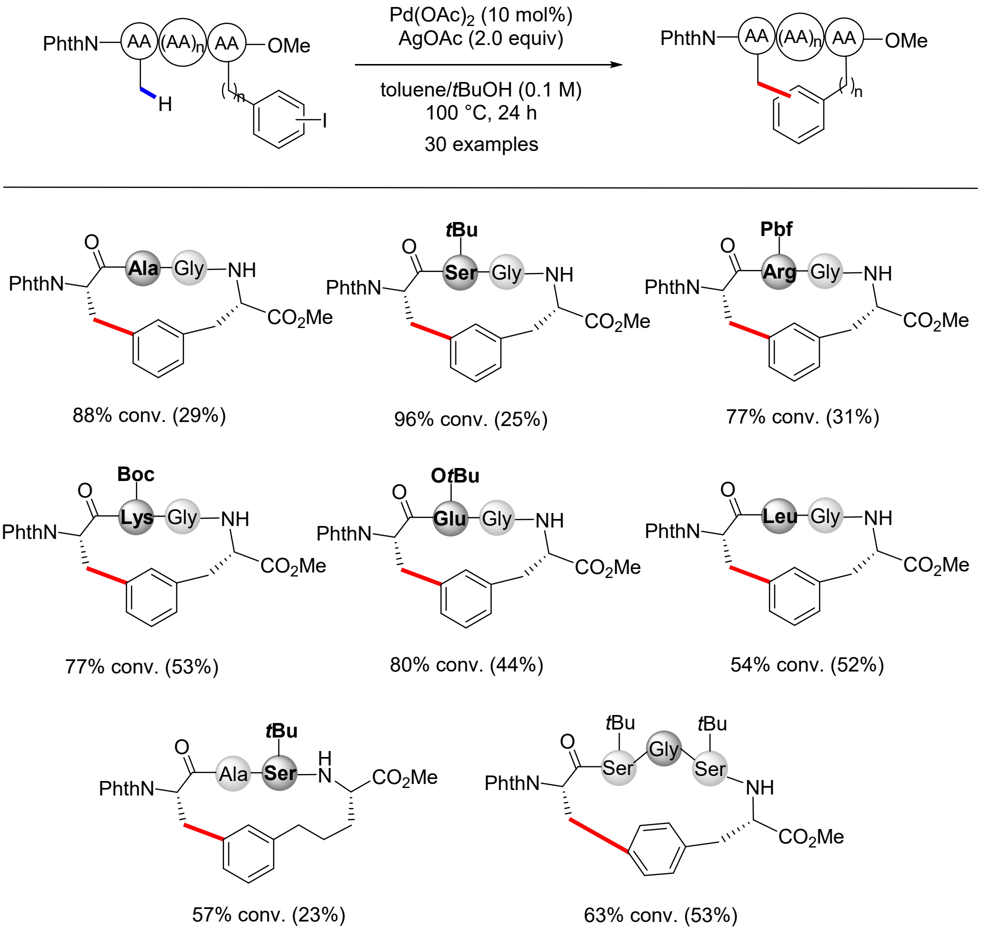


Figure 18. Stapled peptides obtained via Pd(II)-catalyzed intramolecular C(sp^3)–H arylation [83].

Almost at the same time, Wang and co-workers also demonstrated an analogous macrocyclization via the intramolecular β-C(sp^3)–H arylation of amino acids at the *N*-terminus of the peptides, which could proceed smoothly in both solution-phase and solid-phase peptide synthesis approaches (Figure 19) [84]. In this protocol, 1,2-dichloroethane (DCE) was used as the solvent to achieve remarkable efficiency. This approach tolerated a broad scope of peptide substrates, including tetra- and pentapeptides, delivering a diverse variety of polypeptide macrocycles bearing Cβ–Ar cross-links between the β-carbon of amino acids and the aromatic ring of Phe/Trp, with satisfactory diastereoselectivity. Successfully, the authors applied this macrocyclization methodology to the total synthesis of the key fragment in the bioactive natural product celogentin C.

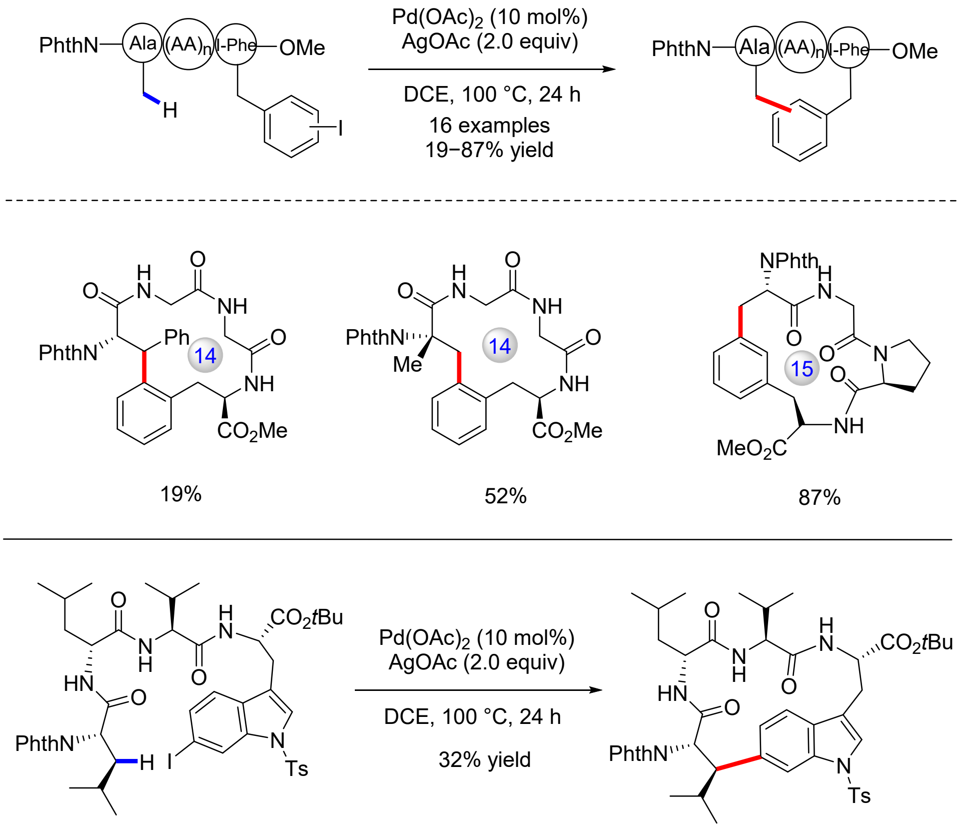


Figure 19. Synthesis of peptide macrocycles via palladium(II)-catalyzed intramolecular C(sp^3)–H arylation [84].

Through the assistance of 8-aminoquinoline (AQ) as the bidentate directing group [85], Chen et al. in 2018 developed a broadly applicable strategy for the efficient synthesis of cyclophane-braced peptide macrocycles from readily accessible linear peptide precursors via the *exo*-type intramolecular β-C(sp^3)–H macrocyclization of diverse alkyl appendants bearing iodinated aromatic side chains or tethered aryl iodides (Figure 20) [86]. The choice of *ortho*-phenyl benzoic acid (oPBA) as the efficacious additive significantly promoted this AQ-directed intramolecular β methylene C(sp^3)–H arylation reaction. Both protected and unprotected amino acid units were compatible with this macrocyclization strategy. Various cyclophane-braced peptide macrocycles of different sizes and shapes were synthesized in moderate to good yields. However, the amide-linked AQ auxiliary was found to be difficult to remove from the peptide macrocycles in this case. Mechanistically, this AQ-directed intramolecular macrocyclization process was proposed to occur through a concerted metalation–deprotonation (CMD) catalytic mechanism. With the assistance of the carboxylate ligand, the reversible β-C(sp^3)–H palladation produced a chelation-stabilized five-membered alkylpalladium(II) species. Subsequently, this putative palladacycle intermediate underwent intramolecular oxidative addition and reductive elimination to afford the expected peptide macrocycles.

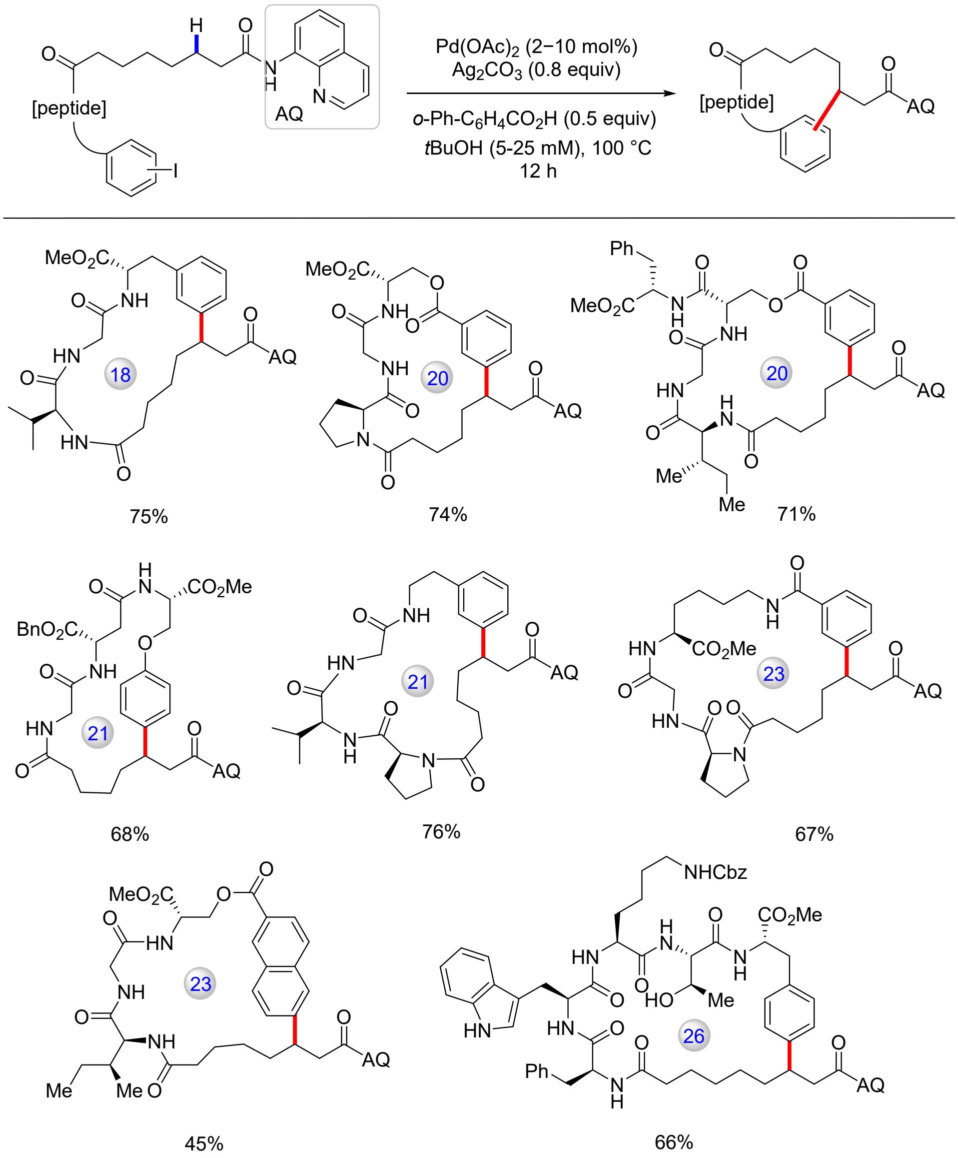


Figure 20. Synthesis of cyclophane-braced peptide macrocycles via palladium-catalyzed intramolecular C(sp^3)–H arylation [86].

By taking advantage of readily accessible and removable *N*,*N*-bidentate picolinamide (PA) auxiliaries, Chen and co-workers in 2019 also described the efficient Pd-catalyzed intramolecular remote γ-C(sp^3)–H arylation of diverse *N*-terminal aliphatic amino acid units via Pd(II)/Pd(IV) catalysis (Figure 21a) [87]. This reaction tolerates γ-C(sp^3)–H bonds at both methyl and methylene positions of peptide substrates. Unprotected peptides bearing diverse free polar side chains were proven to be compatible substrates for this PA-directed C(sp^3)–H macrocyclization protocol, and the cyclization reaction occurred smoothly with high efficiency. Through the typical combination of a Pd(MeCN)$_4$(BF$_4$)$_2$ catalyst and AgOAc additive, 30 examples of this transformation were documented with reasonable yields up to 80%. Encouraged by this success, the same group further elaborated on the efficient synthesis of cyclophane-braced peptide macrocycles via the palladium(II)-catalyzed, AQ-directed *endo*-type intramolecular β methyl C(sp^3)–H arylation reaction with tethered aryl iodides, giving rise to a broad range of cyclic peptides featuring different ring sizes in satisfactory yields (Figure 21b) [88].

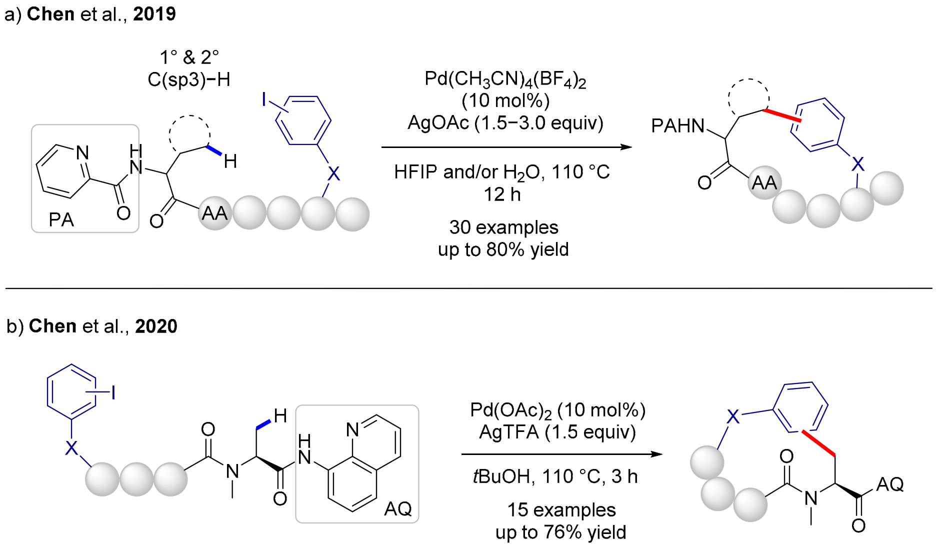


Figure 21. Synthesis of cyclophane-braced peptide macrocycles via intramolecular $C(sp^3)$–H arylation [87,88].

4. Conclusions

In summary, we have witnessed a surge in the use of intramolecular C–H bond activation–macrocyclization reactions to construct polypeptide macrocycles, and to a lesser extent polyketide macrocycles. Despite the remarkable advantages of using C–H activation strategies for the straightforward synthesis of diverse polyketide and polypeptide macrocycles, it is not yet possible to completely avoid the use of substrates bearing alkene or aryl iodide functionalities for the C–H bond activation–macrocyclization reactions. The application of the C–H bond macrocyclization strategy is still an untapped territory, and strategies utilizing transition-metal-free electrocatalytic photoredox C–H bond activation remain to be tested. Most of the reported strategies utilize the aryl $C(sp^2)$–H activation methods to construct macrocycles. Sporadic examples utilizing alkenyl $C(sp^2)$–H bond and alkyl $C(sp^3)$–H bond activation methods have also emerged in recent years. With the surge in activities related to C–H bond activation, more reports utilizing C–H activation strategies for macrocyclization can be envisaged in this fascinating field.

Author Contributions: X.W.: Literature collection and manuscript writing. M.-Z.L.: Literature collection, manuscript writing. and funding acquisition; T.-P.L.: Content design, manuscript revision, project administration, and funding acquisition. All authors have read and agreed to the published version of the manuscript.

Funding: We gratefully acknowledge the financial support from the National Natural Science Foundation of China (no. 22101095) and the "Innovation and Entrepreneurship Talents Plan" of Jiangsu Province (M.-Z. Lu). We also acknowledge the financial support from the Distinguished University Professor grant (Nanyang Technological University); the AcRF Tier 1 grants from the Ministry of Education of Singapore (RG11/20 and RT14/20); and the Agency for Science, Technology, and Research (A*STAR) under its MTC Individual Research Grants (M21K2c0114).

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

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