A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition

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To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201807953
Angew. Chem. 10.1002/ange.201807953

Link to VoR: http://dx.doi.org/10.1002/anie.201807953
http://dx.doi.org/10.1002/ange.201807953

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10.1002/anie.201807953

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Backbone-enabled Directional Peptide Macrocyclization through Late-stage Palladium-catalyzed δ-C(sp^2)-H Olefination

Zengbing Bai, Chuangxu Cai, Zonglun Yu and Huan Wang*[a]

Abstract: C-H activation methods for peptide macrocyclization have the potential to provide peptidomimetics and cyclic peptides with expanded structural diversity. Here, we report the development of a highly versatile peptide macrocyclization strategy via late-stage palladium-catalyzed δ-C(sp^2)-H olefination of phenylalanine residues. This protocol utilizes peptide backbone amides as internal directing groups and allows facile macrocyclization of peptides in the "N-to-C" direction. Combined with our previously developed β-C(sp^3)-H arylation method for peptide macrocyclization in the "C-to-N" direction, we have obtained a pair of palladium-catalyzed reactions that are directionally orthogonal, and demonstrate the first example of one-pot synthesis of bicyclic peptides *via* Pd-catalyzed β-C(sp^3)-H and δ-C(sp^2)-H activation.

Peptides and peptidomimetics have emerged as an increasingly important class of therapeutics with high potency and selectivity.[1] One major driving force for the growing interest of these substances is their capability in regulating protein-protein interactions (PPIs),[2] which have been identified in numerous biological process and highly related to diseases. Compared with native peptides, chemically modified peptides and peptidomimetics often display improved biological activities and pharmacokinetics.[3] Therefore, it is highly desirable to develop strategies for site-specific functionalization of peptides, among which macrocyclization is one of the most prominent methods. Compared to their acyclic counterparts, peptide macrocycles usually have well-defined structures and drug-like properties.[4] Classic methods to generate cyclic peptides include head-to-tail lactamization,[5] internal disulfide[6] or thioether formation,[7] ring-closing olefin metathesis (RCM)[8] and Cu-catalyzed cycloaddition of azides to alkynes.[9] In addition, multicomponent-condensation and S_NAr substitution reactions have recently been successfully applied to peptide macrocyclization.[10] Despite these advances, chemical methods to construct cyclic peptides are still limited compared with synthetic methods for small molecules.[11]

Transition metal catalyzed C-H activation has now become a fundamental strategy to functionalize complex molecules.[12] Recently, several elegant examples of late-stage site-selective C-H functionalization of peptides using Pd catalyst have been achieved, including β-C(sp^3)-H arylation and alkynylation at the N-terminal amino acid by Yu,[13] γ-C(sp^3)-H carbonylation of peptides by Carretero,[14] β-C(sp^3)-H arylation and BODIPY labelling of peptides using internal 1,2,3-triazole moieties as the directing group by Ackermman.[15] As most methods follow a five-membered palladacycle pathway during C-H activation, Shi and co-workers reported a unique example of selective δ-C(sp^3)-H alkylation of peptides through a kinetically less favored six-membered palladacycle by utilizing PA as the directing group.[16]

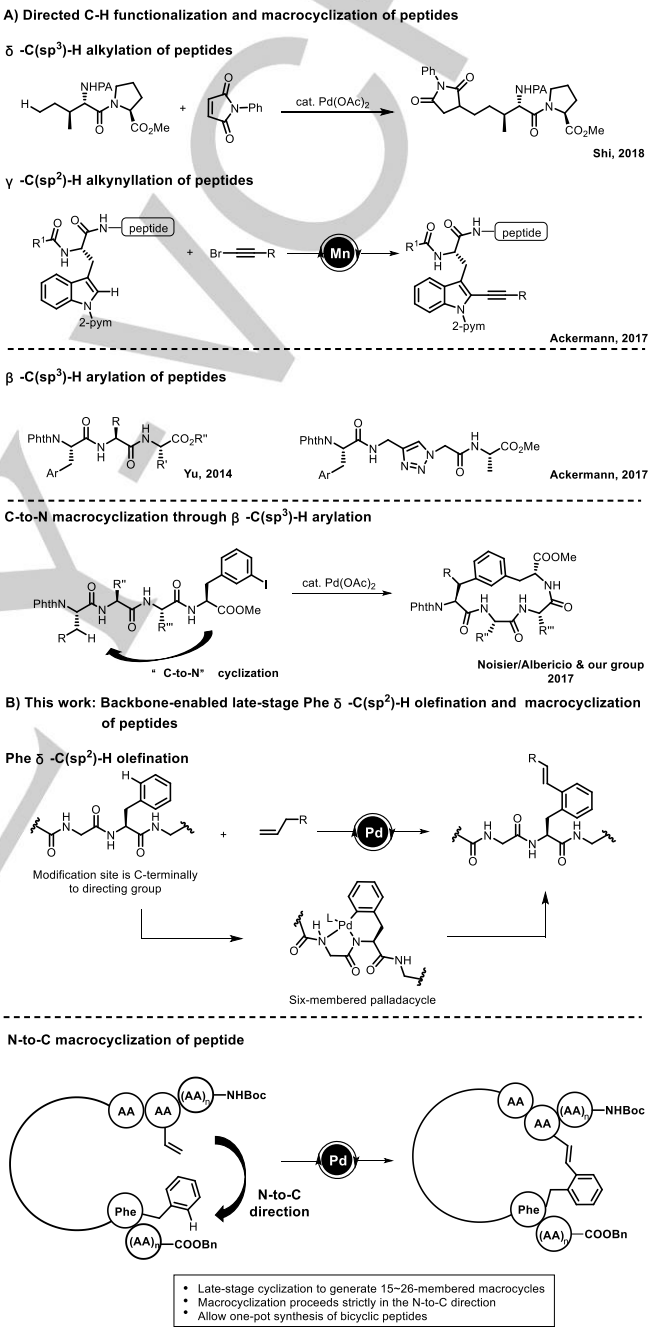

Figure 1. Pd-catalyzed site-selective late-stage δ-C(sp^2)-H functionalization and macrocyclization of peptides enabled by peptide backbone.

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10.1002/anie.201807953

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To achieve peptide macrocyclization, Albericio/Lavilla utilized Pd-catalyzed C-2 arylation of the indole side chain of tryptophans (Trp) by iodo-aryl amino acids to synthesize stapled peptides with aryl-aryl crosslinks.[17] Noisier/Albericio and our group independently developed an intramolecular β-C(sp^3)-H arylation method to construct peptide macrocycles containing βC-Ar crosslinks.[18] In addition, a Mn-catalyzed C-H alkynylation method is developed for late-stage peptide modification and macrocyclization.[19] More recently, Chen and coworkers reported a highly efficient and general strategy to prepare constrained cyclic peptides using 8-aminoquinoline-directed intramolecular arylation of C(sp^3)-H bonds in the presence of Pd catalyst.[20] In continuation of our studies on peptide macrocyclization,[21] we herein report the late-stage Pd-catalyzed δ-C(sp^2)-H olefination of phenylalanine (Phe) residues enabled by peptide backbone, and its application in synthesizing cyclic peptides with unique aryl-alkene crosslinks. Our method utilizes peptide backbone amides that are N-terminally to a Phe residue as internal directing groups (Fig. 1B), and displays broad substrate scope including unactivated alkenes. Furthermore, we show that peptide macrocyclization achieved by this method follows the N-to-C direction. Combined with the previously developed C-to-N peptide macrocyclization through β-C(sp^3)-H arylation, we have obtained a pair of Pd-catalyzed peptide macrocyclization reactions that are directionally orthogonal, and demonstrated the first example of one-pot synthesis of bicyclic peptides using backbone-enabled β-C(sp^3)-H and δ-C(sp^2)-H activation.

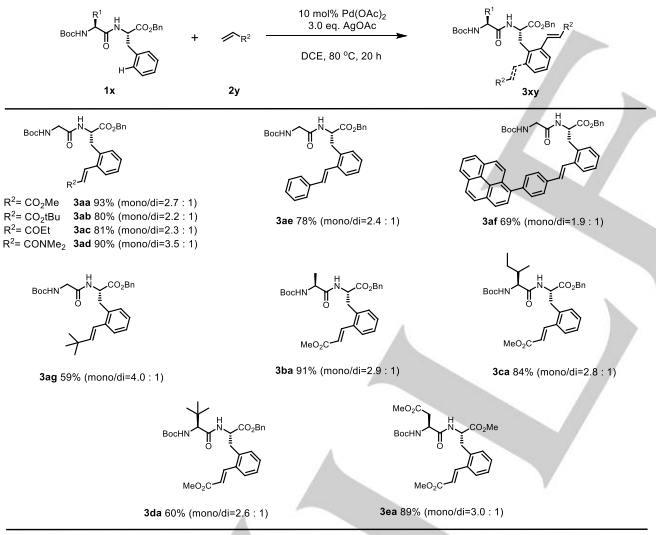

Figure 2. Pd-catalyzed olefination of Phe residues in dipeptide substrates utilizing backbone amides as directing groups. The ratio of mono- and bi-olefination products are shown in parentheses.

We initiated our investigation by employing a dipeptide BocNH-Gly-Phe-COOBn (**1a**) as the model substrate and acrylate methyl ester (**2a**) as the olefination reagent (Fig. 2). Preliminary screenings led to the formation of mono-olefination product (**3aa**) and di-olefination product (**3aa'**) in 93% yield (mono: di = 2.7: 1). NMR analysis of product (**3aa**) revealed that the olefination occured selectively at the δC position of the Phe residue, and the double bond was determined to be in *E*-configuration (Fig. S1-S2). After detailed optimization, we finalized the reaction conditions for the δ-C(sp^2)-H olefination as follows: 10 mol% $Pd(OAc)_2$, 3.0 eq. AgOAc, with DCE as solvent at 80 ºC for 20 h (Table S1).

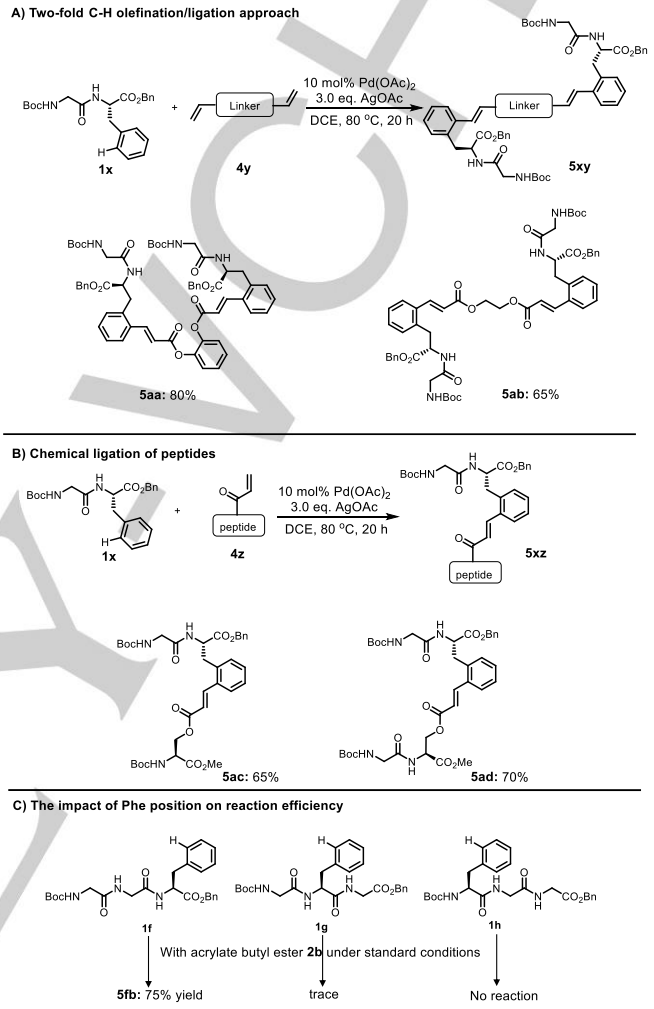

Figure 3. A). Two-fold C-H olefination for the homo-ligation of dipeptides; B). Ligation of amino acids and peptides bearing Phe residues and alkenes. C). Positional effect on the backbone-enabled Phe olefination.

With the optimized conditions in hand, we proceed to evaluate the substrate scope of this peptide backbone-enabled reaction (Fig. 2). Using dipeptide (**1a**) as the model substrate, we first examined a variety of alkenes as olefination reagents. Results showed that both acrylate methyl ester (**2a**) and acrylate *tert*-butyl ester (**2b**) reacted with (**1a**) efficiently, yielding corresponding products in 93% and 80% yields (entries **3aa** and **3ab**). Pent-1-en-3-one (**2c**) and N,N-dimethylacrylamide (**2d**) were also good substrates, resulting in product (**3ac**) and (**3ad**) in 81% and 90% yields, respectively. Pd-catalyzed *ortho*-olefination of arenes with unactivated alkenes is generally challenging.[22] To our delight, substrate (**1a**) reacted smoothly with styrene (**2e**) and 3, 3-dimethylbut-1-ene (**2g**) in good yields (entries **3ae** and **3ag**). Recently, Ackermann and co-workers developed a highly efficient

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Ru-catalyzed method allowing fluorescent labelling of peptides.[23] Our approach successfully install a fluorescent 4-(4-vinylphenyl)pyrene (**2f**) onto dipeptide in 69% yield (entries **3af**). Next, we evaluated the impact of dipeptide sequences on the reaction. The protocol is also compatible with dipeptides containing N-terminal Ala, Ile and t-Leu (entries **3ba**-**3da**), as well as protected amino acids (entry **3ea**). No racemization was observed during reaction (Scheme S1). Together, these results showed that the backbone amides are effective directing groups to facilitate the site-selective δ-C(sp^2)-H olefination of the Phe residue.

Furthermore, the robustness of this olefination method leads to two-fold C-H olefination for the homo-ligation of dipeptide (**1a**) with bis-functional alkenes (**4a**) and (**4b**), delivering tetra-peptides (**5aa**) and (**5ab**) in high yields (Fig. 3A). This result prompted us to utilize this reaction in site-selective ligation of amino acids and peptides to Phe-containing oligopeptides. Alkene-modified serine (**4c**) and dipeptide (**4d**) both reacted efficiently with substrate (**1a**) (Fig. 3B), demonstrating the potential of this chemistry in the direct preparation of peptide conjugates with complex structures in a site-specific manner.

Next, we evaluated whether the position of Phe residue in an oligopeptide would affect the efficiency of the olefination reaction. Three tripeptide substrates (**1f**-**1h**) were therefore synthesized with Phe residue incorporated at the C-, N-terminus or the middle position, and treated with acrylate butyl ester (**2b**). Results showed that only tripeptide (**1f**) was olefinated by acrylate *tert*-butyl ester (**2b**) efficiently, whereas substrates (**1g**) and (**1h**) was unreactive under standard conditions, indicating that two amide bonds N-terminally to the Phe residue are required to enable this reaction. The reaction of substrate (**1h**) fails most likely because for C-terminal amides to facilitate δ-C-H olefination of Phe, a kinetically unfavored seven-member palladacycle need to be formed (Fig. S3). In contrast, two amide bonds that are N-terminally to the Phe residue in substrate (**1f**) could activate the δ-C-H bond by generating a six-membered palladacycle, allowing the reaction to proceed smoothly (Fig. S3).

Encouraged by the success of intermolecular olefination of Phe-containing dipeptides, we further explore the applicability of our method in generating cyclic peptides with unique aryl-alkene crosslinks, which are found in a number of natural products including cyclopeptide alkaloids (Fig. S4).[24] We started with a tripeptide substrate (**6a**) containing an acrylate-modified Ser residue (Fig. 4, Fig. S4). Under standard conditions, substrate (**6a**) reacted efficiently with full conversion, yielding a 15-membered cyclic peptide (**7a**). Tetrapeptides (**6b**) and (**6c**) cyclized with increased efficiency, affording 18-membered macrocycle (**7b**) and (**7c**) in 55% and 40% isolated yields, respectively. Positioning Ala and Leu residues at the third position to the C-terminus has no impact on macrocyclization (entries **7d** or **7e**). Introduction of Pro residue in substrate (**6f**) facilitated the macrocyclization, affording product (**7f**) in 58% yield. When methyl protected Tyr was incorporated into the tetrapeptide substrate (**6g**), intramolecular δ-C(sp^2)-H olefination of Tyr occured selectively to yield macrocycle (**7g**) in good yield, demonstrating the versatility of this method. Next, we expanded the substrate scope to pentapeptide (**6h**) and hexapeptide (**6i**), leading to 21- and 24-membered macrocycles (**7h**) and (**7i**), respectively, in good yields. Structural analysis by NMR revealed that the olefination reaction occurred at the δ-C(sp^2) position of Phe residue, and the resulting double bond is in *E*-configuration in the resulting cyclic peptides (Fig. S5-S6). Next, we challenged our macrocyclization method with unactivated alkenes. A pent-4-enoic acid was conjugated to the side chain of Ser at the N-terminus in substrate (**6j**), and treatment of substrate (**6j**) under standard condition led to the successful production of a 17-membered cyclic peptide (**7j**) in 52% yield, demonstrating the potency of this backbone-enabled macrocyclization method. It is noteworthy that no branched olefination product was observed during the macrocyclization of (**6j**). Finally, we applied our method to the synthesis of a bioactive cyclic RGD sequence, which provided a 26-membered peptide macrocycle (**7k**) in 42% yield. Together, these results demonstrated that the backbone-enable macrocyclization strategy is highly efficient in generating cyclic peptides of various sizes and sequences.

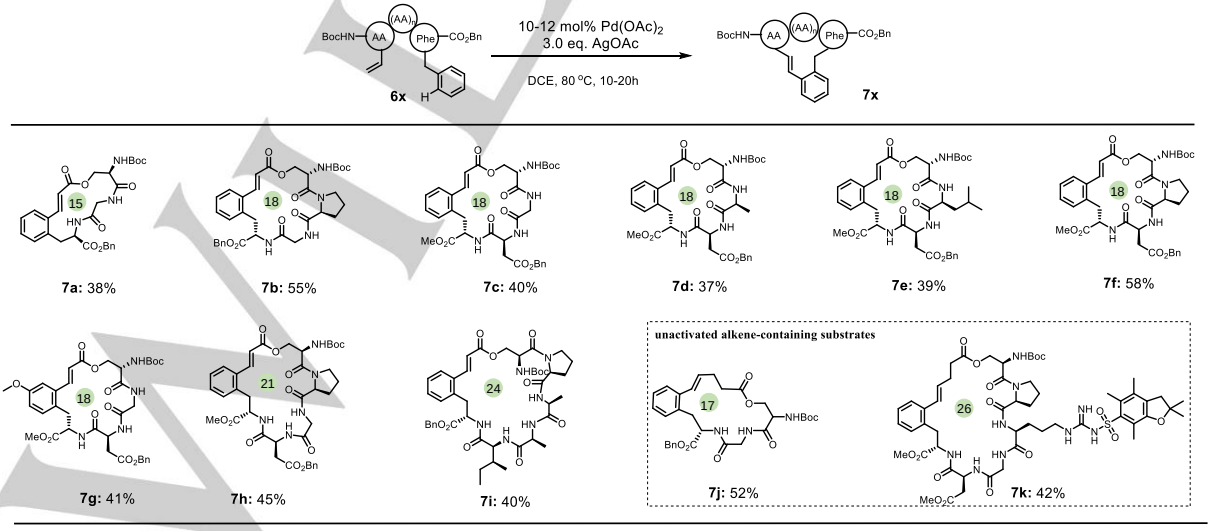

Figure 4. Peptide macrocyclization via late-stage Pd-catalyzed δ-C(sp^2)-H olefination of phenylalanine

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Enzymatic macrocyclization of peptide natural products is often a directional process, which endows highly controlled and regioselective formation of complex ring topologies.[25] The positional effect of backbone-enabled Phe olefination in peptides (Fig. 3C) raises the possibility that the backbone-enabled macrocyclization reaction is directional. Therefore, we synthesized tripeptide (**6b'**) containing the same amino acid composition as peptide (**6b**), but in reverse order (Fig. 5A). Results showed that peptide (**6b**) cyclized smoothly to yield macrocycle (**7b**) (Fig. 4, Fig. 5), whereas peptide (**6b'**) was completely unreactive under standard conditions. Similarly, substrates (**6c'**) and (**6f'**), the reverse peptide sequences of substrates (**6c**) and (**6f**), are also unreactive under standard reaction conditions. These results indicate that the backbone-enabled peptide macrocyclization via Pd-catalyzed olefination of Phe residues can only proceed in the "N-to-C" direction, where the alkene group is N-terminally to the target Phe. The failure of "C-to-N" macrocyclization of peptide (**6b'**) is presumably due to the requirement of generating a kinetically unfavored seven-membered palladacycle for δ-C-H activation of Phe (Fig. S7). Previously, Noisier/Albericio and our group have independently developed a Pd-catalyzed β-C(sp^3)-H arylation method for peptide macrocyclization,[18a, 18b] and our recent studies indicated that this macrocyclization method follows the "C-to-N" direction, in which the iodophenylalanine (I-Phe) is required to be C-terminally to the target Ala residue (Fig. 5A). We propose that such directionality is also determined by the formation of palladacycle intermediates during C-H activation. Following the "C-to-N" direction, the reaction generates a five-membered palladacycle, whereas a kinetically unfavored four-membered palladacycle intermediate is generated when following the "N-to-C" direction (Fig. S7). Thus, the backbone-enabled peptide macrocyclization via β-C(sp^3)-H and δ-C(sp^2)-H activation are directionally orthogonal.

Structurally constrained bicyclic peptides have emerged as an important type of bioactive compounds;[26] however, methods to achieved regioselective synthesis of these compounds are rare.[27] One-pot synthesis of bicyclic peptides are particularly challenging because it generally requires two chemically orthognal reactions for the formation of two ring structures.[27d] We envisioned that peptide macrocyclization through β-C(sp^3)-H arylation and δ-C(sp^2)-H olefination as a pair of directionally orthogonal cyclization reactions (Fig. 5A) may allow one-pot synthesis of bicyclic peptides with high regioselectivity. To examine this hypothesis, we synthesized substrate **9a** containing an N-terminal Ala and *meta*-I-Phe as one pair of reacting groups, as well as a C-terminal Phe and alkene-modified Ser as a second pair (Fig. 5B). Treatment of peptide **9a** under optimized conditions generated a bicyclic product **10a** in 35% isolated yield. NMR analysis indicated that the formation of the two rings are highly controlled in **10a**, and solely generated from the β-C(sp^3)-H arylation of the N-terminal Ala and δ-C(sp^2)-H olefination of the C-terminal Phe (Fig. 5B). This result demonstrates that the Pd-catalyzed C-H activation enabled by peptide backbone is a robust strategy in the preparation of complex peptide macrocycles.

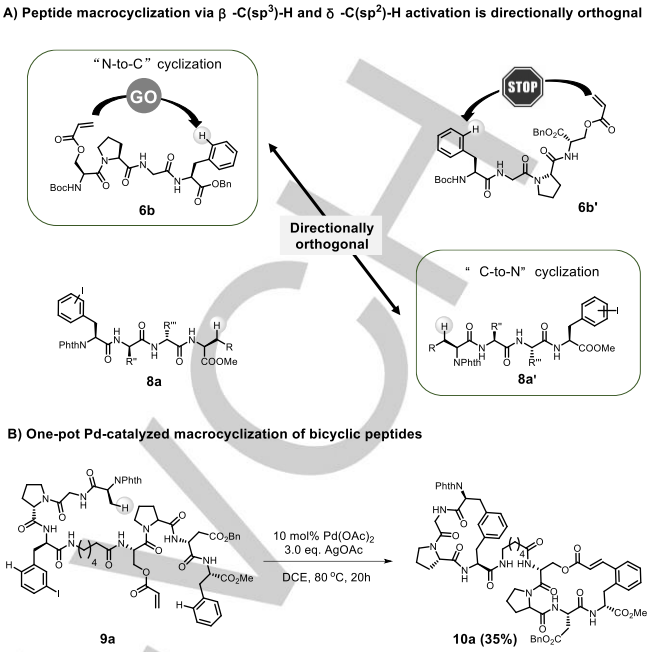

Figure 5. One-pot synthesis of bicyclic peptides through directionally orthogonal Pd-catalyzed macrocyclization.A) peptide macrocyclization via β-C(sp3)-H and δ-C(sp2)-H activation are directionally orthogonal; B) One-pot synthesis of bicyclic peptides using Pd-catalyzed C-H activation.

In conclusion, we have developed a highly versatile late-stage peptide macrocyclization strategy through palladium-catalyzed δ-C(sp^2)-H olefination of phenylalanine residues that are facilitated by the peptide backbone. This method is efficient in peptide modification, ligation and generation of peptide macrocycles of various sizes and sequences. Furthermore, we demonstrate that the backbone-enabled peptide macrocyclization via δ-C(sp^2)-H olefination follows the N-to-C direction, whereas peptide macrocyclization via β-C(sp^3)-H arylation follows the C-to-N direction, providing a pair of reactions that are directionally orthogonal. Such a pair of reactions is applied in the one-pot synthesis of a bicyclic peptide with high regioselectivity. With rational design, the backbone-enabled C-H activation method holds great potential in generating peptide macrocycles of complex topology and related studies are undergoing in our labarotory.

Acknowledgements

This work was supported by the 1000-Youth Talents Plan, NSF of China (Grant 21778030), NSF of Jiangsu Province (Grant BK20160640), the Fundamental Research Funds for the Central Universities (Grant 14380138 and 14380131).

Keywords: cyclic peptide • macrocycle • macrocyclization • palladium catalysis• C-H activation

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10.1002/anie.201807953

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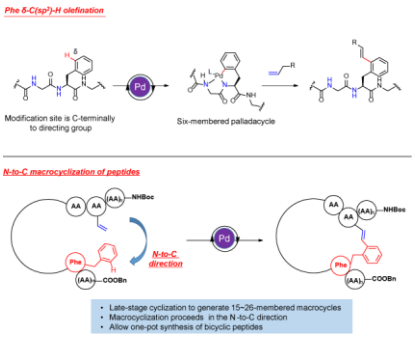
A highly versatile late-stage peptide macrocyclization strategy through palladium-catalyzed δ-C(sp^2)-H olefination of phenylalanine residues has been developed. The backbone-enabled macrocyclization follows the N-to-C direction and allows the one-pot synthesis of a bicyclic peptide.



*Zengbing Bai, Chuangxu Cai, Zonglun Yu and Huan Wang**

Backbone-enabled Directional Peptide Macrocyclization through Late-stage Palladium-catalyzed δ-C(sp^2)-H Olefination

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