INTRODUCTION

Peptides and peptidomimetics are important compounds with broad applications in fields including medicinal chemistry (1–3) and material sciences (4). In particular, cyclic peptides have shown great success as therapeutics by combining favorable properties such as high binding affinity, target selectivity, and capability in regulating protein-protein interactions (5–7). In addition, cyclic peptides with self-assembly properties are important building blocks for organic nanotubes, which have a broad application in artificial ion channels, antimicrobial agents, and electronic materials (4, 8, 9). It is therefore highly desirable to develop efficient chemical methods to prepare peptide-based macrocycles. The strategy of transition metal–catalyzed C–H activation has recently been applied in the functionalization and macrocyclization of peptides, providing new peptide scaffolds that are not easily accessible from traditional methods (10, 11). Seminal examples of late-stage C–H functionalization of peptides using Pd catalysts include β-C(sp³)–H arylation and alknylation at the N-terminal amino acid by Yu and colleagues (12, 13), γ-C(sp³)–H carboxylation of peptides by Carretero et al. (14), δ–C(sp³)–H alkylation of peptides by Shi et al. (15), and cocatalyzed δ–C(sp³)–H activation by Ackermann et al. (16). As a decent demonstration of the compatibility of C–H activation with functional motifs, Ackermann and co-workers (17, 18) developed Pd-catalyzed β–C(sp³)–H arylation that allows boron-dipyromethene (BODIPY) labeling of peptides. In terms of peptide macrocyclization, classic methods include lactamization (19, 20), disulfide formation (21), thioether cross-linking (22), ring-closing olefin metathesis (23–26), and Cu-catalyzed cycloaddition of azides to alkynes (27). As an important addition to the chemical toolbox, transition metal catalysis has achieved peptide stapling through Pd-catalyzed tryptophan C-2 arylation (28–30), β–C(sp³)–H arylation (31, 32), Mn-catalyzed C–H alkylation (33), and δ–C(sp³)–H olefination of phenylalanine (Phe) (34) and N-terminal arylsulfonamides (Fig. 1A) (35). Most recently, Chen et al. (36) reported a powerful strategy to synthesize cyclophane-braced peptide macrocycles through 8-aminquinoline–directed arylation of C(sp³)–H bonds (Fig. 1A).

As our continuous effort in developing chemical methods to synthesize cyclic peptides with high generality and atom economy, we use backbone amides as directing groups to promote Pd-catalyzed late-stage peptide functionalization. Here, we report a peptide-directed method for the functionalization and macrocyclization of arylacetamide-peptide conjugates (peptidoarylacetamides) by Pd(II)-catalyzed late-stage C–H activation. This reaction has a broad substrate scope and provides facile access to a variety of arylacetamide peptidomimetics. The N-acetylated peptides act as internal directing groups, and no external directing groups are required. In addition, this protocol allows macrocyclization of substrates bearing acrylates or unactivated alkenes to generate peptidoarylacetamide macrocycles with unique aryl-alkene cross-links, which are often found in cyclic peptide natural products and challenging to prepare by conventional macrolactamization. Furthermore, we show that the resulting peptide macrocycles containing unique aryl-alkene cross-links exhibit self-assembly properties in organic solvents.

RESULTS

We initiated our investigation by evaluating the utility of dipeptides as directing groups to enable the olefination of aryl acetamides. To establish optimal reaction conditions, we used an ortho-methylbenzylacetamide dipeptide conjugate 1a and methyl acrylate 2a as substrates (Fig. 2, entry 3aa). Detailed optimization studies revealed that the reaction proceeds most efficiently with 1.2 equivalents of methyl acrylate 2a in the presence of 10 mol% Pd(OAc)₂ and 2.0 equivalents of AgOAc in dichloroethane (DCE) at 80°C for 20 hours, affording the ortho-olefination product 3aa in 94% yield (Table S1). Nuclear magnetic resonance (NMR) analysis of product (3aa) indicated that the double bond was in E-configuration (Fig. S1). Replacement of the dipeptide by tLeu methyl ester (Fig. S2, substrate 1a') completely abolished the reaction under standard conditions, indicating that the dipeptide is required to enable the olefination reaction.
Fig. 1. Peptide-directed site-selective olefination and macrocyclization of peptidoarylacetamides through Pd-catalyzed late-stage C(sp²)–H activation.

(A) Macrocyclization of peptides via directed C–H activation. (B) This work: Peptide-enabled late-stage C(sp²)–H macrocyclization of peptidoarylacetamides. AQ, 8-aminoquinoline.

- Late-stage cyclization to generate 14- to 20-membered macrocycles
- Allow incorporation of heterocycles into macrocycles
- The resulting cyclic peptidoacetamides exhibit self-assembly properties
With the optimal conditions in hand, we proceeded to examine the substrate scope of this peptide-enabled reaction (Fig. 2). With dipeptide conjugate (1a) as the model substrate, we first evaluated a variety of alkenes as olefination reagents. Results showed that acrylate ethyl ester (2b) and acrylate butyl esters (2c) and (2d) all reacted with (1a) efficiently, yielding corresponding products in excellent yields [entries (3ab) to (3ad)]. Benzyl acrylate (2e) and pent-1-en-3-one (2f) are also good substrates, resulting in products (3ae) and (3af) in 90 and 75% yields, respectively. The reaction with (ethylsulfonyl)ethane (2g) proceeded with a moderate isolated yield of 56%.

Pd-catalyzed olefination of arenes with unactivated alkenes is generally challenging (37–39). To our delight, substrate (1a) reacted smoothly with styrene (2h), pent-1-ene (2i), 3,3-dimethylbut-1-ene (2j), and vinylcyclohexane (2k) to generate the corresponding products in good yields [entries (3ah) to (3ak)]. Note that no branching products were observed during these reactions. Fluorescent labeling of peptides is highly useful in chemical biology and has been achieved by C–H activation methods (18, 40). Our approach successfully installs a fluorescent 4-(4-vinylphenyl)pyrene (2l) onto dipeptide in 62% yield (entry 3al), further demonstrating the broad scope of this protocol toward olefin donors. Next, we evaluated the impact of aryl substitutions on the reaction. Using methyl acrylate (2a) as the model alkene, substrates with ortho-substitutions, including methoxyl and chloro groups, underwent facile olefination in excellent yields [entries (3ba) and (3ca)]. 2-(naphthalen-1-yl)acetamide and thiophene dipeptide conjugates (1d) and (1e) also reacted with acrylates efficiently, resulting in products (3da) and (3ea) in 95 and 67% yields, respectively. The reaction was further shown to be compatible with various dipeptide and tripeptide substrates [entries (3fa) to (3id)]. To examine the impact of the chirality of peptide substrates, we synthesized (1j) and (1k) containing d-tLeu-Ala and l-tLeu-Ala dipeptides and subjected them to reactions with alkene (2d). Results showed that both reactions proceeded efficiently with similar yields [entries (3jd) to (3kd)]. To address the potential epimerization issue during the reaction, we synthesized substrates (1I) and (1m) and subjected them to reactions with acrylate (2d). Results showed that crude reaction
mixtures of (1l) and (1m) gave distinct retention times when analyzed by high-performance liquid chromatography (fig. S3), indicating that the stereochemical integrity was retained and no epimerization occurred under the reaction conditions. Together, these results demonstrate the versatility of this peptide-directed olefination for peptidoarylacetamides.

On the basis of the high efficiency of this olefination reaction, we further used this method for the homologation of dipeptide (1a) with bis-functional alkenes (4a and 4b) through twofold C–H olefination, delivering tetrapeptides (5aa) and (5ab) in good yields (Fig. 3A). The robustness of this reaction was further demonstrated by the site-selective ligation of amino acids and peptides to peptidoarylacetamides. Alkene-modified serine (4c) and dipeptide (4d) both reacted with substrate (1n) efficiently (Fig. 3B, entries 5nc and 5nd). These results indicate the potential application of this method in the preparation of complex peptide conjugates.

Encouraged by the success of intermolecular olefination of arylacetamide-peptide conjugates, we further explored the applicability of our method in generating cyclic peptides with aryl-alkene cross-links, which are found in bioactive cyclopeptide alkaloid natural products (41, 42). We started our attempt with a dipeptide substrate (6a) containing an acrylate-modified Ser residue. Results showed that this reaction proceeded smoothly to yield a 14-membered cyclic peptide (7a) in 26% isolated yield (55% NMR yield; fig. S4). Structural analysis by NMR and x-ray crystallography revealed that the olefination reaction occurred at the ortho position of methylbenzylacetamide motif, and the resulting double bond is in E-configuration (Fig. 4 and fig. S5). Tripeptides (6b) cyclized with substantially increased efficiency, affording a 17-membered macrocycle (7b) in 65% isolated yield (92% NMR yield; fig. S6). In contrast, conventional macro lactamization of precursor 6b′ under hexafluorophosphate azabenzotriazole tetramethyl uronium (HATU)/N,N-diisopropylethylamine (DIPEA) conditions only led to 12% conversion and trace isolated yield of (7b) (fig. S7). This result demonstrates that this Pd-catalyzed C–H activation method is superior to conventional amide condensation in generating constrained peptidoarylacetamide macrocycles. In addition, tripeptide substrates with Ala and Phe were positioned at the second residue to the N terminus (entries 7c and 7d). Tetrapeptide conjugates are also tolerated in this protocol by generating a 20-membered peptide macrocycles 7e and 7f in moderate yields. Next, we challenged our method by introducing an unactivated alkene in the substrates for macrocyclization. The C-terminal serine was therefore conjugated with pent-4-enoic acid at the side chain hydroxyl group in tripeptide substrates (6g) and (6h). To our delight, treatment of (6g) and (6h) with Pd catalyst resulted in a successful generation of 19-membered peptide macrocycles (7g) and (7h) in 43 and 38% isolated yields, respectively. The relatively low isolated yields of cyclic peptide products is mainly due to the loss of material during purification, because the NMR yields of (7g) and (7h) were 69 and 75%, respectively (figs. S8 and S9). Last,
we applied our method to incorporate heterocycles into cyclic peptides. Thiophene-acetamide peptide conjugate (6i) was therefore synthesized and subjected to cyclization conditions, leading to the production of macrocycle (7i) in 36% isolated yield, further demonstrating the versatility of this peptide-enabled macrocyclization (Fig. 4).

**DISCUSSION**

Crystal structures of peptidoarylacetamide macrocycles (7a) and (7b) reveal their unique self-assembly pattern. From the A-axis view of the crystal packing, macrocycle (7b) adopts a bent conformation (Fig. 5A), in which the carbonyl oxygen of tLeu forms hydrogen bonds with the Ha of NH(Gly) and the αH of tLeu from another molecule. From the B-axis view, molecules of (7b) align perfectly into channels with a width of 6.6 Å (Fig. 5A), where the carbonyl oxygen of Gly forms a hydrogen bond with H4 from the methoxyl group of the adjacent channel. To examine whether this self-assembly of compound 7b is preserved in organic solvents, we performed a concentration-dependent NMR analysis in chloroform. Along with the increase of (7b) concentration, dramatic shift of Hα signal was observed, which is in good correlation with its direct involvement in the intermolecular hydrogen bonding (Fig. 5B). Similarly, the signals of H6 and H7 also exhibited a substantial shift when the concentration of (7b) was increased. In contrast, two other amide hydrogens, Hβ and Hδ, which are not directly involved in hydrogen bonding in the crystal structure, only displayed minor changes in their chemical shifts. Together, NMR analysis suggests that cyclic peptide (7b) has similar self-assembly behavior in organic solvent as in crystal packing. Compound (7a) displays a different packing pattern in the crystal structure by adopting a flat conformation. Molecules of (7a) associate in parallel through the intermolecular hydrogen bonding between amide bonds (Fig. 5C). The aromatic o-methylbenzyl groups stack on each other, presumably driven by π–π interactions. Along the assembly axis, macrocycle (7a) aligned to form a channel with a width of 6.5 Å. The concentration-dependent NMR analysis further suggested their self-assembly in organic solvent, as indicated by the change of chemical shifts of amide NH hydrogens, H6 and Hδ (Fig. 5D). Thus, we demonstrate that peptidoarylacetamide macrocycles containing aryl-alkene cross-links have self-assembly properties in organic solvent.

**CONCLUSION**

In conclusion, we have developed an efficient late-stage peptide functionalization method through Pd-catalyzed C(sp²)–H olefination of peptidoarylacetamides. Furthermore, we demonstrate that the peptidoarylacetamide macrocycles containing aryl-alkene cross-links display unique self-assembly properties in organic solvents and therefore...
Fig. 5. Self-assembly of cyclic peptidoarylacetamides containing aryl-alkene cross-links. (A) Chemical and crystal structures of compound (7b). (B) Concentration-dependent $^1$H NMR analysis of compound (7b) in chloroform. (C) Chemical and crystal structures of compound (7a). (D) Concentration-dependent $^1$H NMR analysis of compound (7a) in chloroform. In the crystal structures, carbon, nitrogen, oxygen, sulfur and hydrogen are shown in grey, blue, red, yellow, and white, respectively. The contacts with a distance less than 3.0 nm are connected in green lines.
have potential applications in peptide-based material science. Our studies highlight the potency of the peptide backbone as an efficient directing group to facilitate site-selective functionalization of peptides and peptidomimetics through palladium catalysis.

**MATERIALS AND METHODS**

**General procedure for the synthesis of peptidoarylacetamides**

Oligopeptides were prepared by standard liquid-phase peptide synthesis. N-Boc oligopeptides were then subjected to 4 M HCl/dioxane for 4 hours at 0°C. Upon completion, the reaction mixture was concentrated and extracted with dichloromethane three times. The organic layer was combined, dried over anhydrous Na2SO4, and concentrated under vacuum. The resulting residue was purified with column chromatography to yield oligopeptide with a free amine at the N terminus. The oligopeptides were then coupled with 2-(o-tolyl)acetic acid to yield corresponding peptidoarylacetamides.

**General procedure for Pd-catalyzed olefination of peptidoarylacetamides**

To a 15-ml sealed reaction tube, dipeptide substrate (0.2 mmol) and olefin (0.24 mmol) were added to the reaction mixture containing Pd(OAc)2 (0.03 mmol) and AgOAc (0.4 mmol) in DCE (2 ml). The reaction was conducted at 80°C for 20 hours and cooled to room temperature upon completion. The resulting sample was diluted with ethyl acetate (5.0 ml), filtered through a Celite pad, concentrated under reduced pressure, and purified by column chromatography.

**General procedure for Pd-catalyzed macrocyclization of peptidoarylacetamides**

Peptidoarylacetamides substrates containing an acrylate-modified Ser residue (0.2 mmol) were mixed with Pd(OAc)2 (0.03 mmol) and AgOAc (0.4 mmol) in DCE (4 ml) in a 15-ml sealed reaction tube. The reaction mixture was stirred at 80°C for 20 hours. Upon completion, the reaction mixture was diluted with ethyl acetate (5.0 ml), filtered through a Celite pad, concentrated under reduced pressure, and purified by column chromatography.

**SUPPLEMENTARY MATERIALS**

Supplementary material for this article is available at http://advances.sciencemag.org/cgi/content/full/5/3/eaaw0323/DC1

Table S1. Optimization of reaction conditions for dipeptide conjugate 1a and methyl acrylate 2a.

Table S2. Crystal data and structure refinement for 7a.

Table S3. Fractional atomic coordinates (×10^4) and equivalent isotropic displacement parameters (Å^2 × 10^3) for compound 7a.

Table S4. Anisotropic displacement parameters (Å^2 × 10^3) for compound 7a.

Table S5. Bond lengths for compound 7a.

Table S6. Bond angles for 7a.

Table S7. Hydrogen atom coordinates (Å × 10^4) and isotropic displacement parameters (Å^2 × 10^3) for compound 7a.

Table S8. Crystal data and structure refinement for 7b.

Table S9. Fractional atomic coordinates (×10^4) and equivalent isotropic displacement parameters (Å^2 × 10^3) for compound 7b.

Table S10. Anisotropic displacement parameters (Å^2 × 10^3) for compound 7b.

Table S11. Bond lengths for 7b.

Table S12. Bond angles for 7b.

Table S13. Hydrogen atom coordinates (Å × 10^4) and isotropic displacement parameters (Å^2 × 10^3) for compound 7b.

Table S14. Crystal data and structure refinement for 7l.

Table S15. Fractional atomic coordinates (×10^4) and equivalent isotropic displacement parameters (Å^2 × 10^3) for compound 7l.

Table S16. Anisotropic displacement parameters (Å^2 × 10^3) for compound 7l.

Table S17. Bond lengths for compound 7l.

Table S18. Bond angles for 7b.

Table S19. Hydrogen atom coordinates (Å × 10^4) and isotropic displacement parameters (Å^2 × 10^3) for compound 7l.

Fig. S1. Determination of the configuration of exocyclic double bond in product 3aa by ^1H NMR (400 MHz, CDC13).

Fig. S2. Substrate 1a is unreactive under standard conditions.

Fig. S3. Investigation of possible epimerization during reactions of substrates 11 (Reaction A) and 1m (Reaction B).

Fig. S4. Determination of reaction yield of substrate 6a by ^1H NMR.

Fig. S5. Determination of the configuration of exocyclic double bond in product 7a by ^1H NMR (400 MHz, CDC13).

Fig. S6. Determination of reaction yield of substrate 6b by ^1H NMR.

Fig. S7. Peptide-directed Pd-catalyzed macrocyclization of substrate (6b) (Reaction A) and macrolactamization of substrate (6b) by condensation (Reaction B).

Fig. S8. Determination of reaction yield of substrate 7g by ^1H NMR.

Fig. S9. Determination of reaction yield of substrate 7h by ^1H NMR.

Fig. S10. ^1H NMR spectrum of macrocycles 7a at various concentrations.

Fig. S11. ^1H NMR spectrum of macrocycles 7a at various concentrations.

Fig. S12. X-ray structure of compound 7a.

Fig. S13. X-ray structure of compound 7b.

Fig. S14. X-ray structure of compound 7l.

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