Construction of Peptide Macrocycles via Palladium-Catalyzed Multiple S-Arylation: An Effective Strategy to Expand the Structural Diversity of Cross-Linkers

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Construction of Peptide Macrocycles *via* Palladium-Catalyzed Multiple *S*-Arylation: An Effective Strategy to Expand the Structural Diversity of Crosslinkers

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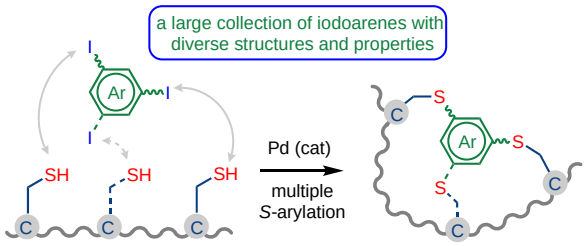
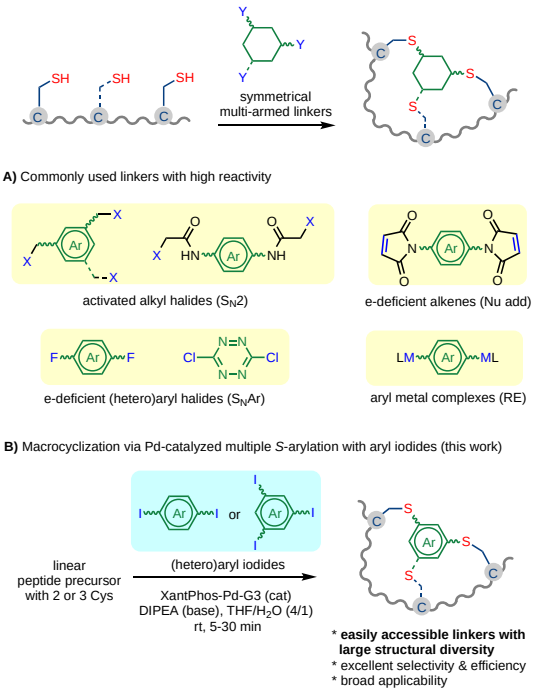


ABSTRACT: While the chemistry for peptide macrocyclization has been greatly advanced, methods capable of introducing crosslinker motifs with large structural diversity are still limited. Herein, we report a simple and versatile method to staple unprotected native peptides with a wide range of easily accessible diiodo and triiodoarene reagents *via* palladium-catalyzed multiple S-arylation of cysteine residues. Iodoarenes with different arene and heteroarene cores can be incorporated into peptide macrocycles of varied ring size and amino acid composition in high efficiency and selectivity under mild conditions.

Synthetic peptide macrocycles are becoming an increasingly valuable source for hit identification in drug discovery.[1] Stapling linear peptide precursors with crosslinking molecules is commonly used to generate the peptide macrocycles.[2] While the crosslinkers were mainly used to constrain the peptide conformation in the early developments of peptide stapling, recent studies showed that linker motifs can play more active roles in constructing sophisticated three-dimensional structures, modulating physiochemical properties or directly engaging with the targets.[3] By far, methods for stapling peptide *via* crosslinking the side chain of cysteine (Cys) residues have enjoyed the most success due to the high reactivity and selectivity of Cys under biocompatible conditions.[4-9] Among the crosslinking chemistry, substitution reactions with reagents bearing multiple halide handles such as benzyl halides and α-halo acetamides for S_N2 substitution and electron-deficient haloarenes for S_NAr reaction have been widely employed.[5,6] Nucleophilic addition reactions with strong electrophiles such as maleimides provide another common tactic.[7] Recently, the chemoselective arylation of cysteine and lysine side chains with organometallic complexes has also been successfully utilized.[8] Despite these significant



Scheme 1. Construction of complex peptide macrocycles via crosslinking cysteines with multi-armed linkers.

advances, the existing methods are not particularly well suited to incorporate linkers with complex structures or to expand the structural diversity of linkers due to the associated synthetic difficulties. Herein, we report a new method to construct peptide macrocycles *via* palladium-catalyzed multiple *S*-arylation of cysteine residues of native peptides with diiodo and triiodoarene reagents. A large number of easily accessible iodoarenes with different arene and heteroarene cores can be incorporated into peptide macrocycles of varied ring size and amino acid (AA) composition in high efficiency and selectivity under mild conditions.

Metal-catalyzed arylation reactions of thiols have recently emerged as a viable strategy for selective modification of peptides in unprotected form and proteins under mild conditions.[10-14] Notably, Pentelute and Buchwald reported the use of stoichiometric aryl-palladium complexes for chemoselective *S*-arylation of Cys residue of unprotected peptides at room temperature (rt).[13] Messaoudi and co-worckers developed a more practical protocol for *S*-arylation of peptides with various aryl iodides using the Xantphos-Pd-G3 catalyst.[14] Recently, we applied Messaoudi's protocol in an intramolecular fashion to construct aryl thioether-bridged peptide macrocycles.[15] This method has also been successfully adapted to make DNA-encoded library of peptide macrocycles. While this intramolecular reaction provides a useful method to generate aryl thioether-bridged peptide macrocycles, it requires the use of peptide precursors carrying a preinstalled iodo handle. To overcome such limitation, we set out to investigate whether two Cys residues of unprotected native peptides can be crosslinked by bis *S*-arylation with diiodoarene reagents under similar Pd-catalyzed conditions.

As shown in Scheme 2, we were pleased to find the reaction of linear peptide PA-Leu-Cys-Ala-Val-Ala-Cys-NH_2 **a** bearing two Cys residues separated by three spacing AA units reacted with 2.0 equiv of 1,4-diidobenzene **1** to give the desired cyclic product **a-1** in 66% isolated yield under the conditions of 10 mol% of Xantphos-Pd-G3 catalyst and 4.0 equiv of diisopropyl ethylamine (DIPEA) base in the mixed solvents of THF and H_2O (4/1) at a concentration of 10 mM at rt for 30 minutes. The *N*-terminus of substrate **a** was capped with a picolinamide (PA) group to enhance the UV absorption in LC analysis. Besides **a-1**, small amounts of disulfide-linked cyclic side product **SP1** and acyclic side product **SP2** with both Cys residues arylated with a 4-iodo-phenyl group were also formed (~15% combined yield based on LC analysis). The yield of product **a-1** slightly dropped when THF was replaced with CH_3CN. EtOH and MeOH co-solvent gave comparable results, while dioxane and hexafluoroisopropanol (HFIP) co-solvents gave considerably lower yield (see supporting information (SI) for details). The peptide substrate **a** was prepared using the standard solid phase peptide synthesis (SPPS) procedure and obtained as a trifluoracetic acid (TFA) salt following the cleavage and deprotection with TFA. The reaction of crude TFA-containing peptide substrate without the addition of base proceeded slowly and completed in about 4 hours under the otherwise identical conditions. The addition of DIPEA greatly accelerated the reaction, allowing the reaction to complete in 10 minutes. The use of other bases such as Et_3N and K_2CO_3 gave similar results (see SI for detailed reaction optimization). Reaction at 1.0 mM concentration of **a** gave similar results. However, significant amount of side product **SP2** was formed (57% LC-estimated yield) when the reaction was carried out at a 50 mM concentration of **a**.

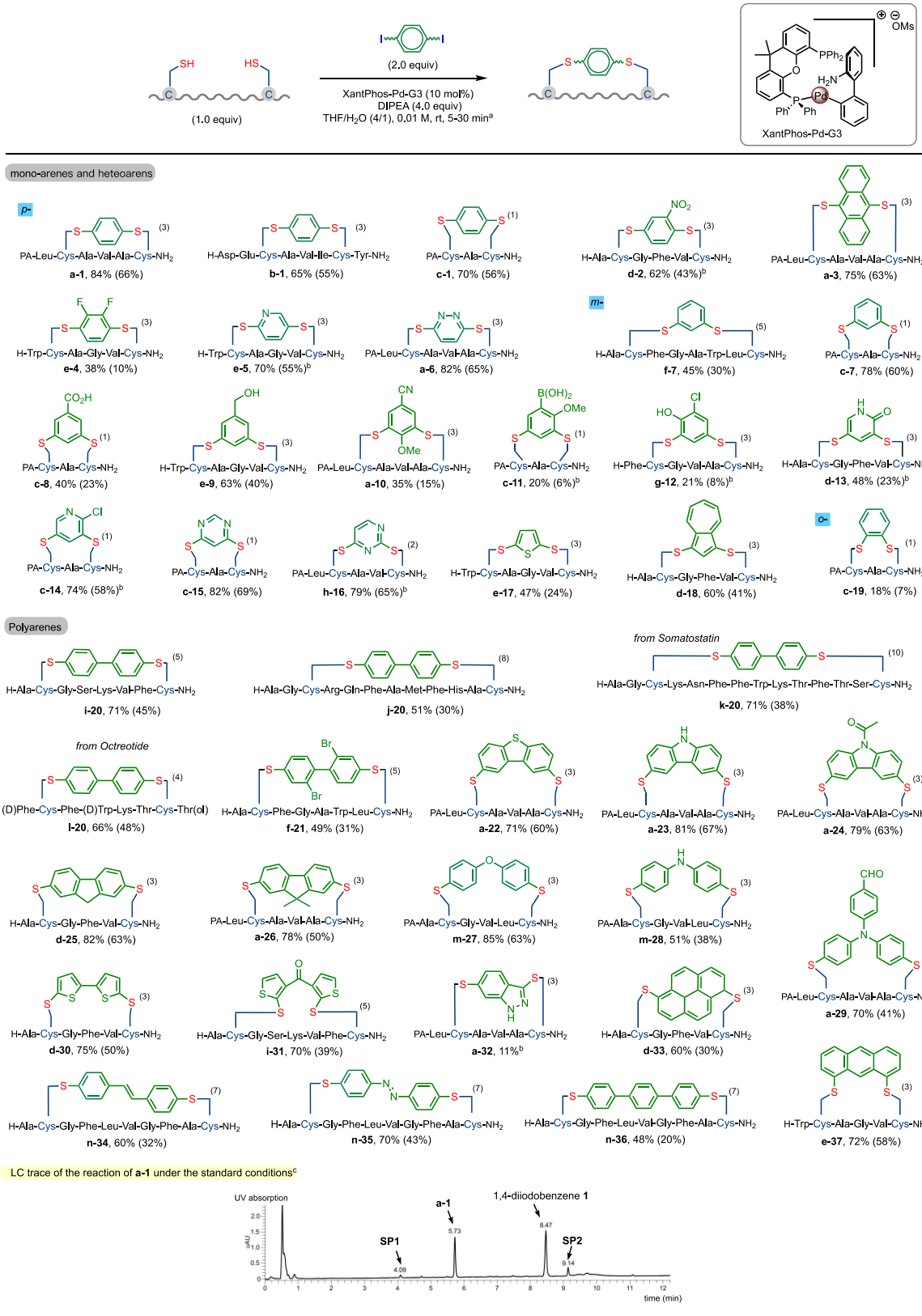
This macrocyclization strategy was then applied to a wide range of peptide substrates and iodoarene reagents. The majority of iodoarenes are commercially available at relatively low costs. Most of these reagents can be prepared from readily available precursors in short steps. As seen in the previous studies, all unprotected proteinogenic amino acid residues such as Asp (**b-1**), Gln (**j-20**), Lys (**k-20**), Ser (**i-20**), Thr (**l-20**), Met (**j-20**), His (**j-20**), Trp (**k-20**), and Arg (**j-20**) were tolerated. A variety of other functional groups such benzaldehyde (**a-29**), boronic acid (**c-11**), nitro (**d-2**), nitrile (**a-10**), azo (**n-35**), and ketone (**i-31**) were well tolerated.

Aryl bromides (e.g. **f-21)** were unreactive. Both *para*- and *meta*-diiodo substituted monoarenes and monoheteroarenes can react well. In contrast, macrocyclization with *ortho*-diiodo arenes were much less effective (e.g. **c-19**). A series of heteroarene motifs such as pyridine (**e-5**), pyridazine (**a-6**), pyrimidine (**c-15**, **h-16**), and thiophene (**e-17**) can be incorporated. Product **d-18** bearing an azulene linker was obtained in good yield. It should be noted that the reactions with asymmetrical diiodides gave the macrocyclic products as a mixture of regioisomers (e.g. **e-5**, **c-14**).

Polyarene linkers of large spans and sizes can also be incorporated into the macrocyclic peptide scaffolds in high efficiency. For example, peptide drugs Octreotide bearing 4 spacing AA units (**l-20**) and Somatostatin bearing 10 spacing AA units (**k-20**) between the two Cys residues were stapled with the 4,4'-biphenyl linker in 48% and 38% isolated yield respectively. Symmetrical linkers such as dibenzothiophene (**a-22**), carbazole (**a-23**, **a-24**), fluorene (**d-25**, **a-26**), diphenyl ether (**m-27**), diphenylamine (**m-28**), bithiophene (**d-30**), bisthiophenylmethanone (**i-31**), pyrene (**d-33**), and anthracene (**e-37**) showed similar reactivities. Product **a-32** featuring an indazole linker was formed in low yield. Incorporation of longer linkers such as stilbene (**n-34**), azobenzene (**n-35**), and terphenyl (**n-36**) worked well for peptide substrates bearing more than 5 spacing AA units between the two Cys residues.

As shown in Scheme 3, peptide substrates bearing three Cys residues can undergo tri *S*-arylation with symmetrical triiodoarene reagents to give the corresponding bicyclic products under the same Pd-catalyzed conditions. For example, reaction of linear peptide PA-Val-Cys-Gly-Leu-Cys-Gly-Pro-Gly-Cys-Gly-NH_2 **p** with 1,3,5-triiodobenzene **38** gave product **p-38** in 45% isolated yield. Monocyclic side products **SP3** and **SP4** were formed in small quantities (~30% combined yield based on LC analysis of the reaction

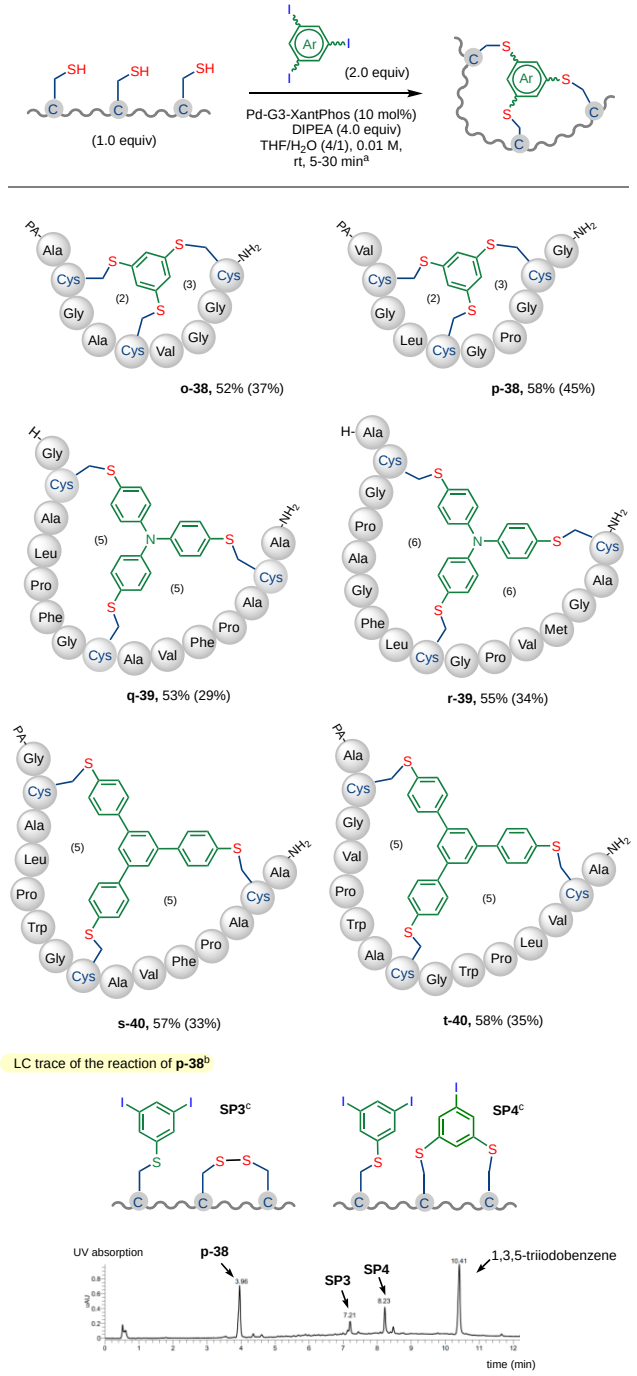
Scheme 2. Construction of monocyclic peptides *via* Pd-catalyzed bis-*S*-arylation of cysteine with diiodoarenes.



a) Reaction was performed with a 10 mM concentration of peptide substrate on a 0.05 mmol scale. LC yields were based on UV absorption of peptides. HPLC isolated yields are shown in parenthesis. The number of spacing AA units between the two Cys residues is shown in parentheses next to Cys side chain. b) Product was obtained as a mixture of regioisomers. c) Catalyst-related species came out during the HPLC column washing period which is not shown here. For more nonpolar peptide substrates, the catalyst-related species could come out during the gradient separation period. See SI for details. Thr(ol): L-threoninol. PA: picolinic acid.

mixture, see Scheme 3 and SI for their structures). Reactions with tri(4-iodophenyl)amine **39** and 1,3,5-tris(4-iodophenyl)benzene **40** gave the corresponding tricyclic products in moderate yields. Reagents **38-40** are commercially available and relatively inexpensive.

Scheme 3. Construction of bicyclic peptides via Pd-catalyzed tri-*S*-arylation of cysteine with triiodoarenes.



a) Reaction was performed with a 10 mM concentration of peptide substrate at a 0.05 mmol scale. LC yields were based on UV absorption of peptides. HPLC isolated yields were shown in parenthesis. The number of spacing AA units between the two Cys residues is shown in parentheses next to Cys side chains. b) Catalyst-related species came during the column washing period which is not shown here. For nonpolar peptide substrates, the catalyst-related species could come out during the separation period. See SI for details. c) Schematic structures of **SP3** and **SP4** based on molecular weight (See SI for details).

In summary, we have developed a practical and versatile method to construct complex peptide macrocycles via palladium-catalyzed multiple *S*-arylation of cysteine residues of unprotected native peptides with diiodo and triiodoarene reagents. A wide range of arene and heteroarene linkers can be incorporated into peptide macrocycles in high efficiency under mild conditions. This method provides a powerful tool to introduce large structural diversity to the crosslinker motifs of peptide macrocycles using readily accessible peptide precursors and linker reagents.

ASSOCIATED CONTENT

Supporting Information.

Additional experimental procedures, LC analysis traces, and NMR spectra for selected compounds are provided. The Supporting Information is available free of charge on the ACS Publications website.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

We gratefully thank NSFC-21725204, NSFC-22071119, and NCC2020FH02 (Nankai University) for financial support of this work. Authors acknowledge also support of this project by CNRS, University Paris-Saclay, and the China Scholarship Council for a fellowship (CSC) to Linhua Shen.

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