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## Handcuffing Peptides by a Key of Gold

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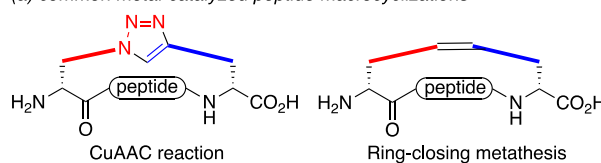
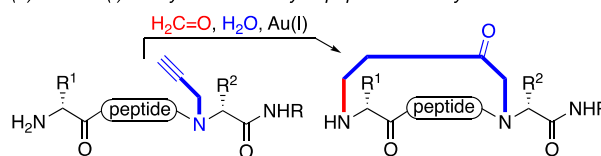
Article Recommendations

Jan H. van Maarseveen

**Mild and efficient macrocyclization of unprotected peptides featuring a backbone propargylic amide was accomplished by a new Au(I)-catalyzed reaction.**

Cyclic peptides are among the most important molecular scaffolds for drug discovery. However, many linear precursor sequences are reluctant to ring closure. As a consequence, there is a continuous need for powerful reactions that are compatible with fully unprotected peptides. In this issue of *ACS Central Science*, the Brik group discloses a gold(I)-catalyzed macrocyclization between the primary amine of the peptide N-terminus or lysine side chain and a backbone amide N-propargyl group.<sup>1</sup>

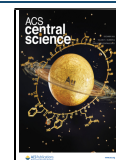
The 20 proteogenic amino acids are the most fascinating molecular building blocks of life. The biological activities of proteins such as enzymes, antibodies, receptors, oxygen transporters, keratin fibers, as well as peptide hormones have nothing in common, other than that these biomolecules are made from the same set of amino acid building blocks. This shows the unsurpassed structural and chemical diversity that is achieved by just a few chemically different side chain moieties. Expansion of the diversity space by the bacterial and fungal nonribosomal biosynthetic machinery even allows the incorporation of other side chain functional groups, *N*-methylated and *D*-amino acids, and, most importantly, cyclization. An ultimate example of a non-ribosomally prepared peptide featuring all these elements is the fungus-derived orally available immunosuppressant drug cyclosporin A. Therefore, it is not surprising that cyclic peptides are popular molecular platforms, especially in pharmacochemical research, due to the combination of their modular construction allowing combinatorial approaches, high selectivities, and even oral availability.<sup>2</sup> Structurally,

*(a) common metal-catalyzed peptide macrocyclizations**(b) new: Au(I)-catalyzed imine-alkyne peptide macrocyclization*

**Figure 1.** (a) Peptide macrocyclizations by the widely used CuAAC or RCM reactions and (b) the new Au(I)-catalyzed imine-alkyne coupling.

cyclic peptides may be placed in between the classical small molecules obeying the rule-of-five and the rapidly emerging biologicals. As a result, the physicochemical properties of cyclic peptides allow targeting of protein–protein interactions (PPIs).<sup>3</sup> Both by the natural biomachinery and via organic synthesis, the presence of reactive moieties at the termini and side chains allows a plethora of different ring-closing reactions. The position of the mutual reactive groups allows several cyclization pathways such as N- to C-terminus, side-chain-to-side-chain, or terminus to side chain. The development of powerful bond-forming reactions that are compatible with unprotected canonical amino acid side chain moieties, such as the copper-catalyzed azide alkyne cycloaddition (CuAAC) and ring-closing olefin metathesis (RCM), gave new opportunities for peptide macrocyclization (Figure 1a).<sup>4</sup> In addition to obtaining high yields, these

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reactions are discriminated by mild reaction conditions and, especially in the case of the CuAAC reaction, without the need for side chain functional group protection.

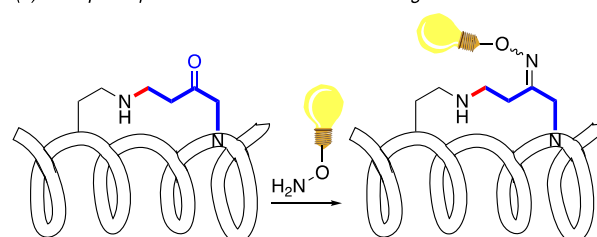
Therefore, it is not surprising that cyclic peptides are popular molecular platforms, especially in pharmacochemical research, due to the combination of their modular construction allowing combinatorial approaches, high selectivities, and even oral availability.

Earlier work by the Brik group has shown the utility of backbone-N-propargyl groups as protective groups that are cleaved by Au(I) catalysis and also as selective amide bond cleavage sites.<sup>5</sup> As reported in this issue, it was found that by tweaking the reaction conditions, cyclization occurs between the propargyl group and the N-terminal amine (Figure 1b). Macrocyclization was accomplished within 20 min at ambient temperature under air in the presence of formaldehyde, some water, and the addition of commercially available (JohnPhos)Au(ACN)SbF<sub>6</sub> complex as the catalyst. In essence, this new Au(I)-catalyzed imine-alkyne coupling inserts a 2-butanone “staple” in between the N-terminus and the propargyl-bearing N atom. After proper protection of the N-terminus, the lysine side chain amine group can be used for efficient macrocyclization. Mechanistic studies suggest that the cationic Au(I)-alkyne complex initially reacts with water resulting in a nucleophilic Au-CH<sub>2</sub>-C(=O)-R species that subsequently attacks the electrophilic N-terminal imine that is formed by condensation of the N-terminus with formaldehyde.

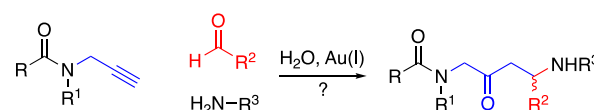
Macrocyclization was accomplished within 20 min at ambient temperature under air in the presence of formaldehyde, some water, and the addition of commercially available (JohnPhos)Au(ACN)SbF<sub>6</sub> complex as the catalyst.

The wide synthetic scope of this new way of peptide macrocyclization is worth mentioning. With the exception of an N-terminal histidine, thus bearing an imidazole moiety, all other unprotected proteogenic amino acids are allowed. Macrocycles were made consisting of 6–17 amino acids corresponding to ring sizes spanning from 20 to 53 atoms.

(a) example of possible selective ketone-labelling via oxime formation



(b) suggested intermolecular Au(I)-catalyzed imine-alkyne coupling



**Figure 2.** (a) The ketone product of Au(I)-catalyzed imine-alkyne stapling may allow selective, unprotected peptide-compatible labeling. (b) An example of the suggested intermolecular Au(I)-catalyzed imine-alkyne coupling.

The icing on the cake was the synthesis of endocyclic 2-butanone analogues of a previously found lys48 ubiquitin chain binding peptide macrocycle that was ring closed via thioether bond formation. Besides potent binding, the 2-butanone cyclized peptide proved to be cell permeable and promoted apoptosis.

So far, the Au(I)-catalyzed macrocyclization only occurs sluggishly when carried out on a solid phase. Although not discussed by the authors, this might be caused by the use of the classical apolar polystyrene resin that is incompatible with water. However, because of the ease of workup but also to exploit the infinite dilution effect promoting intramolecular reactions, finding the optimal solid phase conditions would be desirable.

The Brik group developed this reaction specially to carry out efficient peptide macrocyclizations. The resulting endocyclic *N*-(4-amino-2-oxobutyl)amide tethers contain a secondary amine and ketone that are amenable to further selective transformations. This may be interesting for their use as labeling sites in stapled/stitched peptides aimed at disturbing PPIs (Figure 2a). In such peptides, the staple/stitch parts stabilize helicity and are not involved in the binding process positioning such a label outside the binding groove. Another opportunity lies in combining the reactive moieties for RCM and the Au(I)-catalyzed alkyne imine reaction in the same peptide for the synthesis of multicyclic peptides. As with the CuAAC and RCM reactions, the Au(I)-catalyzed coupling of imines with propargylic amides may also work efficiently in an intermolecular fashion (Figure 2b). Furthermore, instead of formaldehyde, other aldehydes and even ketones may possibly be used as imine precursors not only introducing additional groups but also interesting stereochemical features. These options are left

fully unexploited in the current paper of the Brik group, thus opening up new horizons outside the peptide field.

Another opportunity lies in combining the reactive moieties for RCM and the Au(I)-catalyzed alkyne imine reaction in the same peptide for the synthesis of multicyclic peptides.

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#### Notes

The author declares no competing financial interest.

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