Highly Efficient Cyclization Approach of Propargylated Peptides via Gold(I)-Mediated Sequential C–N, C–O, and C–C Bond Formation

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**ABSTRACT:** A rapid and efficient cyclization of unprotected N-propargylated peptides using the Au(I) organometallic complex is reported. The method relies on the activation of the propargyl functionality using gold(I) to produce a new linkage with the N-terminus amine at the cyclization site. The presented method features a fast reaction rate (within 20 min), mild conditions, chemoselectivity, wide sequence scope, and high yields (up to 87%). The strategy was successfully tested on a wide variety of 30 unprotected peptides having various sequences and lengths, thus providing access to structurally distinct cyclic peptides. The practical usefulness of this method was demonstrated in producing peptides that bind efficiently to Lys48-linked di- and tetra-ubiquitin chains. The new cyclic peptide modulators exhibited high permeability to living cells and promoted apoptosis via binding with the endogenous Lys48-linked ubiquitin chains.

**INTRODUCTION**

Targeting protein−protein interactions (PPIs) with small molecules remains a challenging endeavor. Druglike small molecules are too small to bind large protein interfaces, while large molecules have various drawbacks, among them poor membrane permeability, which limits access to intracellular targets. Cyclic peptides have gained great interest, not only due to their restricted conformation and cellular stability but also due to their high efficacy in targeting PPIs. Therefore, the development of synthetic strategies for creating cyclic peptides has been of great interest for many research groups. However, their synthesis remains a challenging and formidable task mainly due to the entropically disfavored cyclization step, which requires a suitable conformational rearrangement of the linear peptide.

The common methods for metal-free peptide cyclization, lactamization, lactonization, and disulfide bond formation, suffer from low efficiency due to side reactions, e.g., intermolecular polymerizations, which then necessitates, e.g., the introduction of turn inducers into the peptide sequence or performing the reactions at a low concentration. To further expand peptide cyclization methods toward increased reaction efficiency and structural diversity, several research groups have exploited the unique reactivity of transition metals (e.g., Cu, Ru, and Pd). This includes click chemistry, alkene metathesis, heteroatom coupling, and more recently C–H activation. However, some of these methods suffer from harsh conditions (e.g., reaction temperatures of 100 °C), a requirement of long reaction times (24−48 h), a requirement of sacrificial oxidants, low yields, and the necessity of protecting groups on the amino acid side chains, which hamper the practical synthesis of the desired target.

Gold complexes are underutilized in peptide synthesis in general and for cyclization in particular, as well as in the bioconjugation and biofunctionalization of macromolecules. Unlike other transition metals, gold could bring several advantages as it is less expensive and redox neutral, and some of its complexes are air- and moisture-insensitive and biologically friendly. Recently, we developed a gold-mediated depropargylation of N-propargylated backbone amides to facilitate the synthesis of peptides and proteins with highly challenging sequences. Moreover, when reversing the order of the amino acids at the propargylated site containing a Gly residue, this led to amide bond hydrolysis at this site. Given the unique reactivity of gold toward alkynes, where the reaction reactivity and selectivity could be tuned via the careful choice of the ligand and additives, we sought to further explore gold chemistry in peptide synthesis and functionalization. In particular, we were interested in developing an efficient method for peptide cyclization, motivated to generate a new type of
bonding, which could affect the activity, conformation, and permeability of cyclic peptides.

Herein, we report on the development of a new and chemoselective cyclization method of fully unprotected peptides by employing a gold-mediated cyclization of propargylated peptides in the presence of formaldehyde. Our method was applied to generate cyclic peptides with structurally diverse peptide macrocycles having different ring sizes, irrespective of the peptide sequence and the position of ring forming center. We further applied our method to generate cyclic peptides that modulate Lys48-ubiquitin (Ub) chains in vitro and cellulary and subsequently induce apoptosis of cancer cells.

RESULTS

Homogeneous Au(I) catalysts have been employed in a plethora of organic transformations. The strong Lewis acidity of the cationic Au(I), coupled with its potential to stabilize cationic reaction intermediates, imparts unique reactivity to such catalysts in addition to their tolerance for a wide range of functional groups and reaction conditions.25 We hypothesized that, by changing gold ligands, we might be able to change the reactivity and selectivity of the gold metallic complex toward the propargyl group. We envisaged that the attack of the water molecule at the $\beta$-position of the Au-activated alkyne would trigger the cyclization with the electrophilic N-terminal imine—generated from formaldehyde, followed by a proto-deauration event affording the cyclized product (Figure 1a).

To this end, we applied standard Fmoc-SPPS to synthesize a model peptide composed of H$_2$N-GLYRAG(prop)G, following our published procedure.23 With this model peptide in hand, we examined the cyclization reaction by testing various cyclizing conditions using different metal complexes, solvents (used as is from commercial bottles), and temperatures in the presence of formaldehyde (Figure 1b). Of the tested metal complexes, the (JohnPhos)Au(ACN)SbF$_6$ showed initially promising results at room temperature in DMF or dioxane (Figure 1b, entries 1 and 2). The reaction efficiency improved by changing the solvent to a mixture of a 1:1 ratio of DMF/dioxane, still at room temperature. Next, we attempted to improve the reaction by changing the temperature and reaction time (Figure 1b, entries 3 and 4). After several rounds of optimization, we found that carrying out the reaction using (JohnPhos)Au(ACN)SbF$_6$ in DMF/dioxane (1:1) and in the presence of 20% v/v formaldehyde at 37 °C gave, within 20 min, the desired product in respectable yields (Figure 1b, entry 5; and the SI, Figure S1). We hypothesized that, as the amount of water increases, the conversion and efficiency improved by changing the solvent to a mixture of a 1:1 ratio of DMF/dioxane, still at room temperature. Next, we attempted to improve the reaction by changing the temperature and reaction time (Figure 1b, entries 3 and 4). After several rounds of optimization, we found that carrying out the reaction using (JohnPhos)Au(ACN)SbF$_6$ in DMF/dioxane (1:1) and in the presence of 20% v/v formaldehyde at 37 °C gave, within 20 min, the desired product in respectable yields (Figure 1b, entry 5; and the SI, Figure S1). The effect of water addition on the reaction outcome was also studied (SI, Figure S39). We performed the reaction by adding 10%, 20%, and 30% (v/v) water to the reaction conditions and observed that, as the amount of water increases, the conversion of the starting material decreases. Notably, a cyclization reaction on resin support under the described conditions was carried out, and it was found that the reaction could proceed on resin support. However, the desired product was formed only in 20% while the water addition product was obtained in 65% along with unidentified side products (SI, Figure S38).

Mechanistic Insights. To gain insights into the reaction mechanism, we attempted to trap the reaction intermediates by blocking the N-terminal amine, which should prevent the cyclization step. Therefore, we synthesized the model peptide Me$_2$N-GGLYRAG(Prop)G (I), where the N-terminus amine is modified with the dimethyl substitution. Peptide I was subjected to our optimized reaction conditions, and the crude mixture was analyzed by HPLC-ESI mass spectrometry (Figure 2a). This analysis revealed three peaks with clear masses, corresponding to the $\sigma$-bonded (JohnPhos)Au-acetylide complex of the model peptide and $\pi$-/ $\sigma$-bonded dinuclear Au(I)-JohnPhos complex intermediates (Figure 2a). The third mass corresponds to the Markovnikov’s water addition product 2. Upon treatment of the reaction mixture with diithiothreitol (DTT), to quench and release the gold complexes from the peptide, the reaction mixture gave 2 as the sole product (Figure 2a), which was further confirmed by NMR (SI, Pages S41–S50).

Based on the data that we collected alongside the experimental observations and assessment of the literature’s proposed mechanisms of propargyl activation by gold,26–29 we...
propose the following mechanism for the cyclization reaction (Figure 2b). Initially, formaldehyde reacts with the N-terminus amine to form an imine species, while gold coordinates with the propargyl to form the $\pi$-alkyne gold(I) complex $I$. Next, deprotonation of the terminal alkyne by the counterion $\text{SbF}_6^{-}$ would generate $\sigma$-alkynyl gold(I) complex $II$. A second gold coordination leads to the formation of dinuclear $\sigma, \pi$-digold(I) alkyne complex $III$. It is unclear which complexes, $II$ or $III$, are the catalytically active species that leads to the Markovnikov water addition to form the intermediate $\beta$-oxopropyl-Au(I), $IV$. Subsequently, complex $IV$ could be trapped by the electrophilic imine, via $C-C$ bond formation, to obtain the desired cyclization product $V$. Eventually, protodeauration would provide the cyclized product, $VI$. The presence of intermediate $IV$ can also be attributed to the observed water addition product $VII$, in the cyclization reaction as well as in the case of the N-terminally blocked amine 1.

Scope of the Cyclization Site. To examine the effect of the cyclization site on the reaction efficiency, we prepared three focused libraries of model peptides. The first library consisted of 10 peptides containing different N-terminal amino acids (H$_2$N-AAAA-GLYRA(prop)G, $\text{AA}_{8}$ = Gly, Ile, Asp, Ser, Phe, Arg, His, Trp, Glu, and Cys), (Figure 3a1). All peptides were subjected to our optimized cyclization conditions, and the corresponding cyclic peptides were generated in moderate to high conversion yields (43–81%). Notably, in the cases of Arg and Trp, we observed an increase in the peak corresponding to the water addition product $VII$, along with the cyclized product, while for
His, we observed only the water addition product VII. This might be due to the N-terminal amino acid directly affecting the coordination of Au(I) and therefore its reactivity. In such cases, VII could result due to the coordination of the side chain (e.g., imidazole) and stabilizing intermediate IV. As a result, this would lead to rapid proto-deauration at the α-carbon center site, creating more of the water addition product at the expense of the cyclized one (Figure 2b).

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We then decided to investigate propargylation sites on the cyclization step (Figure 3a2), assuming that the amino acids at
this site might affect the cyclization due to steric hindrance and conformational factors. Therefore, model peptides containing a propargylated amide at AA−Gly junctions with different amino acids (AA: Ile, Asp, Ser, Ala, and Arg) were synthesized and tested. Exposing each one of these peptides to our optimized conditions led to the formation of the desired cyclized products in 58−71% conversion yields. In principle, amino acids such as Ile and Ala exert steric hindrance while Asp and Ser could strongly coordinate with the gold, which could inhibit the reaction. However, it appears that none of these has affected the reaction outcome to any great extent, which demonstrates the broad tolerance and the efficiency of the method for peptide cyclization.

Subsequently, the effect of the altered propargylation sites, i.e., Gly−AA, on the cyclization reaction was also examined. The amino acids Ile, Asp, Ala, and Arg were substituted in and tested (Figure 3a3). Our results indicate that the sterically hindered amino acid Ile worked well and provided the product in 64% conversion yield. Furthermore, model peptides containing Asp or Arg, potentially metal coordinating amino acids, were cyclized to give the desired product in 67% and 63% yields, respectively (Figure 3a3).

Considering the large effect of some of the N-terminal amino acids on the reaction yields [e.g., His (Figure 3a1)], we sought to investigate their effect in the middle of the peptide sequence. Therefore, a series of model peptides were tested, each one bearing a different amino acid in the middle of the sequence [Asp, His, Trp, Cys, and Cys protected with acetamidomethyl (Acm)] . The reactions of all tested peptides proceeded smoothly to give the cyclized products in 51−85% conversion yields. Notably, in this series of model peptides, the His amino acid also worked well relative to its position at the N-terminal site (SI, Figure S26). To our surprise, Cys was also well tolerated, despite the potential for the thiol group to strongly

Figure 4. (a) Cyclization through the Lys−ε-amine of the Fmoc-NH-GLYKRAG(prop)G model peptide followed by Fmoc deprotection. (b) Analytical HPLC−mass analysis for the cyclization reaction of Fmoc-NH-GLYKRAG(prop)G. Peak a corresponds to the starting material with observed mass 1079.6 ± 0.2 Da (calcd 1079.9 Da). Peak b corresponds to cyclization product with the observed mass 1110.0 ± 0.0 Da (calcd 1109.9 Da). Peak c corresponds to Fmoc-deprotected cyclic product with the observed mass 887.6 ± 0.1 Da (calcd 887.9 Da); yield based on an LC-MS analysis of the crude reaction mixture. (footnote b) isolated yield. (c) Selective cyclization through N-terminal amine in the presence of different protecting groups of Lys ε-amine. Yield based on LC-MS analysis of the crude reaction mixture. (JohnPhos)Au(ACN)SbF₆ (2.0 equiv).
coordinate various metals and form stable complexes. When Cys(Acm) was used, this led to product formation along with Acm removal, (SI, Figure S29).

We then investigated the effect of the chain length on the cyclization reaction by fixing the propargylated junction and N-terminal amino acid, but changing the number of residues in each model peptide (Figure 3b). Such model peptides, having

Figure 5. (a) Cyclization of peptide 4 (left). Analytical HPLC−mass analysis for the cyclization reaction of 4 (right). Peak a corresponds to the starting material with observed mass 1674.5 ± 0.2 Da (calcd 1675.8 Da). Peak b corresponds to cyclization product with the observed mass 1705.2 ± 0.0 Da (calcd 1705.8 Da). (JohnPhos)Au(ACN)SbF₆ (2.0 equiv). (b) Binding curve of FITC-labeled 9 to Di-Ub K48. The data points were fitted using an equation representing a one-site noncooperative ligand binding model \( Y = \frac{B_{\text{max}} \times X}{K_d + X} \), where \( X \) is ligand (9) concentration, \( Y \) specific ligand binding, \( B_{\text{max}} \) maximum specific ligand binding, and \( K_d \) dissociation constant. The \( K_d \) value of 5.40 ± 0.40 nm was determined. All measurements were performed in triplicate. (c) Live-cell uptake of cyclic peptides 9 and 10: (c, panels a and e) Hoechst signals from live cells. (c, panels b and f) FITC signal from the cyclic peptide 9 and 10, respectively. (c, panels c and g) Hoechst and FITC signals merged. (c, panels d and h) Bright-field images. The experiment was repeated in duplicates. (Scale bar 10 μm.) (d) Induction of apoptosis in HeLa cells by cyclic peptide 6 (bars represent standard error). (e) Structure of the cyclic peptides 5−10.
6–17 amino acids in the sequence, would cover ring sizes of 20–53 atoms. Our results showed that the peptide length did not have a noticeable effect on the efficacy of the cyclization reaction. The peptide with the 6 amino acids (20-membered ring) gave the cyclic product in 77% conversion yield (Figure 3b, entry 1). Similarly, model peptides with 9, 12, and 17 amino acids participated well in the reaction and provided the cyclized products in 80%, 60%, and 87% conversion yields, respectively (Figure 3b, entries 2–6).

**Cyclization of Lys Containing Peptides.** Next, we turned our attention to model peptides with a free Lys residue in their sequences. As excess amounts of formaldehyde and stoichiometric amounts of the gold complex were employed, we anticipated that the presence of free Lys ε-amine in the sequence could compete with the N-terminus amine in the cyclization reaction. Indeed, when examining the reaction of two model peptides, one with dimethylated N-terminus amine and the other with dimethylated ε-amine on the Lys side chain, the two amines reacted to form the cyclic peptide with comparable kinetics. To this end, we decided to use protecting groups on the N-terminus amine or protection of the Lys side chain to direct the cyclization step.

First, we prepared a model peptide with Fmoc-protected N-terminal amine (Fmoc-GLYKRAG(prop)G) and subjected it to our reaction conditions. Within 20 min, we obtained the cyclized product through the Lys side chain with the Fmoc protecting group still intact. Subsequently, the Fmoc protection was successfully removed in situ with 20% piperidine (Figure 4a,b).

For the case of Lys side chain protection, we prepared two model peptides each with a different protecting group: GLYK(ivDde)RAG(prop)G and GLYK(N3)RAG(prop)G. Each model peptide was exposed to our conditions to produce the cyclic peptide through the N-terminus amine, within 20 min (Figure 4c). Eventually, the GLYK(ivDde)RAG(prop)G macrocycle was subjected to hydrazine to remove the Lys protection. In this case, we observed the removal of ivDde followed by hydrazonic formation with the ketone moiety (SI, Figures S31–S33).

**Synthesis of Cyclic Peptide Modulators of Ub Chains.** Recently, our group discovered cyclic peptides which are capable of binding specifically Lys48-linked Ub chains and therefore modifying in vitro and in vivo their activities.33–36 Ub chains were used as targets for the RaPID system (Random Nonstandard Peptide Integrated Discovery) to select for high-binding cyclic peptides. Despite our successful design and screening, the cyclization chemistry is largely limited to the thioether linkage.37,38 Preparing new analogues of the cyclic peptide using different cyclization methods could further influence their cell permeability, activity, and pharmacological properties. Hence, we synthesized the propargylated form of our lead peptides, DwLYLDSGWDWIG(Prop)G, 3; and GWFDLFLYWFVAY(Prop)G, 4, and cyclized them using our current Au(I)-mediated cyclization method to obtain the corresponding cyclic peptides 5 and 6, respectively (Figure 5a).

With both peptides in hand (5 and 6), we examined the binding efficiency using our fluorescence-based competitive assay.36 We observed a 32% increase in the binding affinity for Lys48-linked tetra-Ub chains and nearly 42% for Lys48-linked di-Ub chains compared to the cyclic peptide having the thioether linkages [ClAc (7) and m-ClBz (8)].

Encouraged by these in vitro results, we explored the cellular uptake and apoptosis efficacy of these new cyclic peptides in living cells. To this end, the cyclic peptide was fluorescently labeled with FITC (9), and for comparison, we used our previously reported FITC-labeled cyclic peptide (10). Both cyclic peptides were incubated for 4 h with HeLa cells at only 5 μM concentration, and the live cell analysis by CLSM showed no significant differences in the cellular uptake between them (Figure 5c). Both cyclic peptides 9 and 10 were efficiently distributed into the cell cytoplasm and nucleus. We also assessed cell apoptosis in the presence of the cyclic peptide, 6, using a Cytek Aurora flow cytometer and showed a similar induction on apoptosis in HeLa cells, upon 24 h of treatment, to that of peptide 8 (Figure 5d).

**Conclusion**

We have developed a new and effective method for cyclization of propargylated peptides using a gold(I) complex. The reaction was performed in the absence of side chain protecting groups and was tolerant to various proteogenic functional groups. Moreover, the reaction proceeded under mild conditions and required relatively short times to give the desired product in respectable yields. The synthetic utility of the presented method was demonstrated by the development of new cyclic peptide modulators for Lys48-linked di-Ub chains with an enhanced binding ability compared to their parent compound. These cyclic peptides showed cellular uptake and promoted apoptosis of cancer cells.

Considering the vast integration of cyclic peptides in numerous fields including bioimaging, material science, and therapeutics, the expansion of the chemical toolbox of reactions and strategies enables access to and synthesis of various interesting cyclic peptides. Our peptide cyclization method can potentially improve the properties of both existing and succeeding natural or non-natural cyclic peptides to push the boundaries in terms of utility and efficacy and maximize the chances of creating effective cyclic peptide-based therapeutics for a variety of PPI targets.

**Associated Content**

**Supporting Information**

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscentsci.1c00969.

Experimental data and characterization data; a discussion on materials, peptide synthesis, experimental methods, cyclization reactions, HPLC and mass spectrometry analyses; and figures showing the synthesis of peptides and HPLC, and 1H NMR, and 13C NMR spectra (PDF)

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Notes
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