Total Chemical Synthesis and Investigation of Modified Linker Histone H1.2 and HP1α Utilizing Ru catalyst

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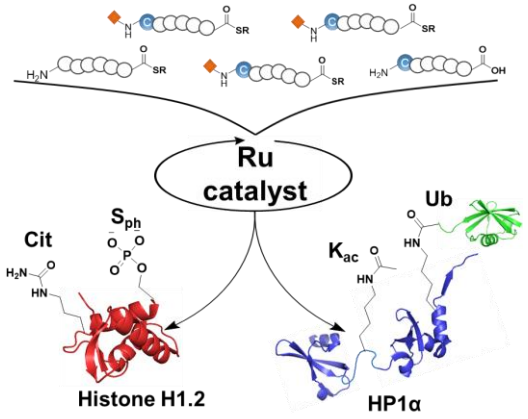
Keywords: Chemical Protein Synthesis; Ru catalyst; Post-Translational Modification

Chemical protein synthesis has facilitated the preparations of target proteins bearing site-specific post-translational modifications (PTMs).[1] Recently, applications of metal complexes for protein synthesis have been focused using those transformative powers, but significant amounts of metal complexes were required to achieve chemical reactions on proteins. Therefore, the synthetic strategy based on metal-catalyzed reactions on proteins has been demanded to avoid wasting expensive organometallic compounds and minimize the possibility of the absorption of metal on proteins.

Here, we report one-pot multiple peptide ligation strategy assisted by an organoruthenium catalyst, which showed more than 50-fold catalytic activity than previous palladium complexes, to eliminate cumbersome purification steps and synthesize proteins of interest with PTMs efficiently. Utilizing the ruthenium catalyst, we accomplished chemical synthesis of heterochromatin factors, histone H1.2 and heterochromatin protein 1α (HP1α), bearing various patterns of PTMs such as phosphorylation, ubiquitination, citrullination. We found that the citrullination at R53 in H1.2 reduced the stability of chromatosomes due to lack of the electrostatic interaction between Arg and DNA. Furthermore, we identified a key phosphorylation region in HP1α to control its binding toward DNA. It was envisaged that our strategy using Ru chemistry would facilitate the preparation of a variety of biologically significant proteins with PTMs and contribute to the elucidation of biological phenomena.



1) V. Agouridas *et al*., *Chem. Rev*. **2019**, *119*, 7328−7443.